Swine as a Model for Influenza A Virus Infection and Immunity

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Abstract

Influenza A viruses (IAVs) infect a variety of hosts, including humans, swine, and various avian species. The annual influenza disease burden in the human population remains significant even with current vaccine usage, and much about the pathogenesis and transmission of influenza viruses in humans remains unclear. Thus, animal models are a fundamental tool for influenza research to understand mechanisms of virulence and to develop more efficacious vaccines and forms of prevention or treatment. The choice of experimental model to be used should be based on the species characteristics and similarities to humans, and how the limitations of each host interfere the least with the parameters studied. Influenza virus infection in swine has many similarities with that in humans: the same subtypes are endemic in both species, there has been repeated exchange of viruses between these hosts, the clinical manifestation and pathogenesis are similar, and there is a similar distribution of IAV receptors in the respiratory tract. Considering these common characteristics, and the similarities between humans and swine in terms of genetics, anatomy, and physiology, pigs represent an excellent yet often overlooked model for biomedical research and the study of IAV infection.

Key words: animal model; human; immunity; infection; influenza A virus; swine

Introduction

Influenza A viruses (IAVs) belong to the family Orthomyxoviridae and are classified according to the subtypes of their major surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA). To date, 16 HA and nine NA subtypes have been isolated from the wild waterfowl natural host, and new subtypes recently identified in bats suggest that other natural reservoirs might exist (Fouchier et al. 2005; Yoon et al. 2014). IAVs infect a large variety of host species, and several hosts become endemically infected with adapted lineages, including pigs, domestic poultry, horses, dogs, and humans (Webster et al. 1992).

IAV strains have different host specificity, due to the binding affinity of the HA to sialic acid receptors on the host cell among other factors (Neumann and Kawaoka 2006). However, pigs are susceptible to both avian and human influenza viruses (Kida et al. 1994). Thus, pigs are considered important hosts in the ecology of influenza and have been pointed out as key in the generation of novel viruses (Scholtissek et al. 1985). The reason for this susceptibility is thought to be largely due to the expression of receptors to both avian and human influenza viruses in the porcine respiratory tract (Ito et al. 1998). A similar distribution of IAV-binding receptors was reported for human airways (Shinya et al. 2006), a feature that has been associated with the transmission of IAV between humans and pigs (Imai and Kawaoka 2012). Such bidirectional transmission can be exemplified by the swine-origin pandemic H1N1 in 2009 (Garten et al. 2009). The similarities do not stop there: IAV endemic in swine worldwide are of
the H1N1, H1N2, and H3N2 subtypes; and viruses circulating in humans in the past decades have been predominantly of H1N1 and H3N2 subtypes, although H2N2 and H1N2 subtypes have caused pandemics and epidemics in humans, respectively. Influenza was first reported in pigs at the same time as the 1918 “Spanish Flu” human pandemic (Koon 1919), and recent data confirm that swine and human H1N1 viruses evolved from the Spanish flu strains and remain genetically related (Smith et al. 2009a; Van Reeth et al. 2012). Moreover, human seasonal H1N1 and H3N2 have repeatedly been transmitted to pigs throughout the years (Nelson et al. 2014), emphasizing the parallel influenza infection dynamics in these two species. Additionally, nearly all major swine lineages around the globe are antigenically connected to human seasonal H1N1 and H3N2 isolated throughout the past three decades due to interspecies transmission (NS Lewis, unpublished data).

Much about the characteristics, prevention, and treatment of the disease caused by IAV in humans remains unclear, and studies using the natural host present obvious limiting factors. The onset of a new pandemic in the 21st century underscored the need for development of broadly efficacious vaccines and new effective forms of treatment. Thus, animal models can be used to replicate intrinsic mammalian factors involved with influenza infection and transmissibility, as an alternative to reduce the deficiencies that can be present for in vitro models. Many animal species, including pigs, have been used to research the diverse traits of influenza (Barnard 2009; Thangavel and Bouvier 2014; van den Brand et al. 2014). The ample susceptibility of swine as a natural host and the common attributes of influenza infection observed in pigs make this species a good model for the study of influenza in humans. In this review, we summarize the role of the pig as an experimental model for human influenza virus infection research and vaccine development, describing factors that make this species a good candidate for such use.

Influenza in the Human Host

Human influenza disease epidemics occur with seasonal characteristics, predominantly during cold months of temperate climates. Seasonal influenza manifests as the sudden onset of mild respiratory symptoms within 1 to 2 days of infection. Symptoms include dry cough, pharyngitis, and nasal discharge and congestion, in addition to systemic symptoms such as fever, anorexia, lethargy, headache, and myalgia (Taubenberger and Morens 2008). Not all infected patients will develop symptoms; however, viral shedding can be detected even in asymptomatic individuals (Memoli et al. 2014). The disease is usually uncomplicated and limited to the upper respiratory tract, but immunocompromised patients with underlying medical conditions (e.g., cardiac, metabolic, or pulmonary disease) are at a greater risk of developing pulmonary complications that can result in rapid progression to primary viral pneumonia or a recrudescent bacterial pneumonia (Memoli et al. 2014; Treanor 2010). Risk factors for complicated seasonal influenza virus infection include advanced age and comorbidities such as diabetes, cardiovascular disease, immunosuppression, or pregnancy (Taubenberger and Morens 2008). Occasionally, novel viruses are introduced into the human population for which there is no pre-existing immunity, resulting in widespread infection of pandemic proportions and higher case rates of pulmonary disease and hospitalization (Morens and Taubenberger 2011).

Variant IAV is the designation given to swine-origin influenza viruses that infect humans on sporadic occasions; however, these cases typically have limited human-to-human transmission (Myers et al. 2007). Approximately 40 cases of human infection with swine-lineage viruses were detected in the United States from 1990 to 2011 (Jhung et al. 2013; Shinde et al. 2009; Shu et al. 2012). In contrast, a swine-origin H3N2 (H3N2v) that contained the matrix gene from the 2009 pandemic virus infected more than 340 people, mainly children, raising concerns in the public health sectors regarding population immunity and viral transmissibility (Epperson et al. 2013; Jhung et al. 2013). In these cases, most people reported mild illness with symptoms similar to those of seasonal influenza, but an increased rate of conjunctivitis was observed (Jhung et al. 2013).

Influenza in the Swine Host

Swine IAVs are a primary cause of respiratory disease in pigs, resulting in widespread infections and great economic burden to producers, particularly when associated with other common swine pathogens. In the past decade, the dynamics of swine influenza virus ecology has made an abrupt expansion of genetic variation, leading to the circulation of many distinct genetic and antigenic viruses that further complicates the control of the infection in pigs (Anderson et al. 2013; Vincent et al. 2008). As a result, more than 10 different genetic H1 and H3 clusters are co-circulating in North American pigs (Anderson et al. 2013). Contrary to the sporadic dead-end zoonotic transmission of swine viruses to humans, reverse-zoonotic events that led to sustained onward transmission have been relatively frequent in swine, contributing to the rich diversity of IAVs in pigs (Nelson et al. 2014). The H3N2 viruses that became established in pigs in Europe in the early 1970s (de Jong et al. 2007) and in North America in the late 1990s (Zhou et al. 1999) were of human origin. More recently, H1 viruses of human origin were introduced to pigs in the early 2000s and contribute to the great genetic diversity that characterizes swine influenza viruses in the United States (Anderson et al. 2013; Vincent et al. 2009). In early 2009, a novel influenza virus (H1N1pdm09) became widespread in the human population (Garten et al. 2009). This reassorted virus had never been detected in pigs but possessed a unique composition with genes related to North American triple-reassortant swine viruses (PB2, PB1, PA, HA, NP, NS) and Eurasian H1N1 swine viruses (NA and M) (Smith et al. 2009b). This human-adapted swine-origin virus has been shown to efficiently infect and transmit among pigs, resulting in clinical disease and viral replication similar to that of endemic influenza (Brookes et al. 2010; Vincent et al. 2010). Similarly, the H3N2v recently isolated from humans (Epperson et al. 2013), a swine-origin virus with the M gene from the H1N1pdm09, showed virulence in pigs similar to endemic swine H3N2 viruses (Kitikoon et al. 2012).

Swine influenza can be characterized as epidemic forms of disease that spread rapidly through the herd following seasonal patterns or as endemic forms that can be detected year-round with varying degrees of disease, the latter being observed more frequently in the past decade (Janke 2013; Rajao et al. 2014). Comparable to the disease in humans, the onset of clinical signs starts approximately 24 to 72 hours after infection, with fever, lethargy, anorexia, and consequent weight loss. Laredo or abdominal breathing, coughing, and nasal discharge are common signs; and conjunctivitis, rhinitis, and sneezing may also be observed (Richt et al. 2003; Van Reeth et al. 2012). Without concomitant infections, the disease progresses rapidly and recovery generally starts 5 to 7 days after infection. Similar to human infections, the degree of pathology depends on the animal individual factors, such as age, immune status, and concurrent infections (Van Reeth et al. 2012).
Animal Models for Human Influenza

Animal models are used to more completely replicate host factors and conditions in which they respond similarly to humans, in ways that cannot be achieved with in vitro models. The choice of which species to use should consider characteristics such as housing requirements, amenability to be handled experimentally, costs, availability, genetic homogeneity, and similarity to humans. Many animal species have been used to study human influenza, including mice, rats, hamsters, guinea pigs, ferrets, dogs, cats, nonhuman primates, and pigs (Barnard 2009; Thangavel and Bouvier 2014; van den Brand et al. 2014).

Mice (Mus musculus) are the most widely used species to study influenza pathogenesis and antiviral therapy due to availability, low cost, and the extensive number of specific reagents available (Bouvier and Lowen 2010; Thangavel and Bouvier 2014). In general, mice are susceptible to influenza A infection; however, adaptation of human viruses is required to result in detectable clinical disease (Thangavel and Bouvier 2014). This may be explained by the lack of human influenza virus receptors in the mouse respiratory tract (Ibricevic et al. 2006). Mouse-adapted viruses are typically used at lethal doses and result in severe disease with lethargy and anorexia, which leads to weight loss and death (Tripp and Tompkins 2009). Another deficiency in the murine model is the lack of shedding in infected mice (Bouvier and Lowen 2010), which renders it inadequate for transmission studies.

Ferrets (Mustela putorius furo) are naturally susceptible to many human IAVs without the need for prior adaptation and, thus, have a major role in influenza research (Buchman et al. 1995; Thangavel and Bouvier 2014). Infection of ferrets with seasonal influenza viruses is usually restricted to the upper respiratory tract and results in influenza-like illness characterized by fever, nasal discharge and congestion, anorexia, lethargy, and sneezing (Maher and DeStefano 2004; Smith et al. 1993). Unlike mice, ferrets shed virus and are an important tool for transmissibility and adaptation studies (Herlocher et al. 2001). Although ferrets’ airways have many resemblances to the human respiratory tract, including their sialic acid repertoire and sneezing reflex (Tripp and Tompkins 2009), the higher costs and limited commercial availability of ferrets, in addition to fewer species-specific immune reagents available, can make this a less-than-perfect model (Bouvier and Lowen 2010; Thangavel and Bouvier 2014).

A model used for influenza virus research more recently is the guinea pig (Cavia porcellus). Similar to the murine model, it has commercial availability and low cost; and the small size makes the guinea pig easy to handle and care for (Thangavel and Bouvier 2014). They are readily infected with human viruses, and there are many similar traits between the respiratory tract of guinea pigs and that of humans (Bouvier and Lowen 2010; Thangavel and Bouvier 2014). Guinea pigs, similar to ferrets, can transmit virus through contact or droplet spread and can be an alternative to models for influenza transmission studies (Lowen et al. 2006, 2014). However, clinical manifestation seems to be reduced in this species, depending largely on the strain of guinea pig used (Lowen et al. 2006). Similar to the ferret model, there are limited reagents available for the species (Thangavel and Bouvier 2014).

Using animal models for human diseases, such as influenza, helps to elucidate the mechanisms involved in the pathogenesis and provides information that can be useful for therapeutics and vaccine development. However, it is crucial that the results can be extrapolated to humans. Mice are the most widely used species for biomedical research but, unfortunately, the murine model often does not faithfully mimic the relevant human conditions. Thus, better animal models may be indicated for addressing specific research questions. A comparison of the most commonly used models for influenza research is shown in Table 1.

The Pig as an Experimental Model of Influenza

Swine (Sus scrofa), as one of the first animals domesticated, are a valuable model for translational research and human health. Their similarities to humans in terms of size, genetics, anatomy, dietary habits and feeding patterns, physiology, and social behavior make the pig an excellent model for nutrition (Mitchell 2007), diabetes mellitus (Bellinger et al. 2006), skin physiology (Simon and Maibach 2000), cystic fibrosis (Rogers et al. 2008), and cardiovascular disease (Türk et al. 2005), among others. The publication of the swine genome (Groenen et al. 2012; Schook et al. 2005) has been fundamental for the establishment of the species as a research model, and the continuous improvement in methods to generate genetically modified and cloned pigs has increased their use for many agricultural and biomedical purposes in recent years (Fan and Lai 2013). The pig genome has a similar size and complexity to the human genome, with higher sequence homology than that of rodents and higher chromosomal structure similarity than many other species (Humphrey et al. 2007; Thomas et al. 2003).

The swine respiratory tract is an excellent model for human respiratory diseases and therapeutics, with remarkable similarities in the tracheobronchial tree structure, lung physiology and size (Judge et al. 2014; Swindle et al. 2012), and also regarding the number of airway submucosal glands (Choi et al. 2000). The lungs of pigs and humans are highly lobulated: swine have three lobes on the left side and four on the right, whereas humans have three right and two left lobes (Judge et al. 2014; Swindle et al. 2012). The bronchial tree distribution is similar to that of other mammal species, although the right apical lobe in swine is directly connected to the trachea (Nakakuki 1994). The upper respiratory tracts of pigs and humans are also anatomically similar, although the morphology of the porcine airways is more cartilaginous and varies somewhat according to age and breed (Judge et al. 2014). Moreover, the immune parameters of pigs closely resemble those of humans, with chemokines and the IL-10 family most comparable (Dawson 2011). The swine immune system is well characterized, although much is still to be understood, with many established methodologies and tools (Meurens et al. 2012). Continuous efforts are being made to phenotype immune cell populations in pigs (Piriou-Guzylack and Salmon 2008).

Because the same IAV subtypes are endemic in pigs and humans (H1N1 and H3N2, in addition to H1N2 in swine), and taking into account the similarity of clinical disease and pathogenesis, swine represent an excellent animal model to study influenza infection. Additionally, pigs are naturally susceptible to some strains of human IAV, especially the H1N1pdm09, and human viruses or human-origin gene segments frequently adapt to efficiently transmit among pigs as described above.

Comparative Pathogenesis of Influenza Virus Infection in Human and Swine

Virus-specific Factors in Influenza A Virus Infection

The HA plays a major role in determining the host range of influenza viruses, particularly due to its involvement in host cell receptor recognition and entry. The influenza HA binds to oligosaccharide receptors that contain terminal sialic acid (SA)
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Humans</th>
<th>Mice</th>
<th>Ferrets</th>
<th>Guinea Pig</th>
<th>Swine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptibility</td>
<td>Natural host: H1N1, H3N2, and H2N2 subtypes are endemic</td>
<td>Natural host: H1N1, H2N1, and H3N2 subtypes are endemic</td>
<td>Requires adaptation to the species</td>
<td>Susceptible</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Receptors</td>
<td>α-2,6- and α-2,3-linked SA receptors in the respiratory tract and a mixture of α-2,3SA and α-2,6SA receptors in the lower respiratory tract</td>
<td>α-2,3-linked SA receptors in the respiratory tract</td>
<td>Similar to humans</td>
<td>Similar to humans</td>
<td>Similar to humans</td>
</tr>
<tr>
<td>Clinical manifestation</td>
<td>Congenital pharyngitis, nasal discharge, fever, anorexia, lethargy</td>
<td>Similar to humans</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Transmissibility</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
<td>High</td>
<td>Limited</td>
</tr>
<tr>
<td>Commercial availability</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Husbandry practices</td>
<td>High</td>
<td>Medium; medium size, requires more space</td>
<td>Easy; small size</td>
<td>Easy; small size</td>
<td>Easy; small size</td>
</tr>
<tr>
<td>Cost</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Genetic manipulation</td>
<td>N/A</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Availability of tools and reagents</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Limited</td>
</tr>
</tbody>
</table>

Abbreviation: N/A, not applicable.

Human influenza viruses preferentially recognize receptors with SA attached to galactose via an α-2,6 linkage (Gambaryan et al. 1997; Stevens et al. 2006), whereas avian viruses preferentially recognize SA linked to galactose via α-2,3 linkages (Rogers and Paulson 1983). In humans, α-2,6SA receptors are expressed mainly on ciliated cells of the upper respiratory tract, and a mixture of both α-2,3SA and α-2,6SA receptors are found in the non-ciliated epithelium of the lower respiratory tract (Nicholls et al. 2007; Shinya et al. 2006). In pigs, expression patterns of SA receptors are similar to those of humans, with abundant expression of human-like receptors on the tracheal epithelia and gradual increase in α-2,3SA expression toward the lower respiratory lining (Nelli et al. 2010; Van Poucke et al. 2010). Nevertheless, different influenza viruses seem to have specific binding patterns to different tissues of the human respiratory tract (Chutinimkitkul et al. 2010; van Riel et al. 2006).

In addition to the sialic acid linkage itself, the structure of underlying glycan receptors, such as size, shape, and chain length, is also important to influenza virus attachment to host cells and might be involved in receptor specificity, efficient replication, and transmission (Gambaryan et al. 2005). The structural topology of sialylated glycans was suggested to be associated with adaptation of HA to receptors in the human respiratory tract since human-adapted viruses were shown to bind to long α-2,6 sialylated glycans with a specific topology, whereas nonadapted avian viruses did not (Chandrasekaran et al. 2008). Gulati and colleagues (2013) investigated the binding specificity of seasonal H3N2 IAV isolated from 1968 to 2012, and revealed that none of the viruses tested had the same binding specificity and avidity to the glycans assessed, yet all were equally fit to infect and transmit in the human population. Similarly, different human, swine, and avian influenza viruses were shown to have variable specific binding profiles to natural glycans in the swine lung, often efficiently binding to both α-2,3SA and α-2,6SA-linked receptors; and none of the viruses tested interacted with sialylated O-glycans or glycolipid-derived glycans (Byrd-Leotis et al. 2014). Sialylated N-glycans have been shown to mediate, although they are not required for, IAV entry into host cells, as receptor-mediated entry was reduced in the absence of N-glycans (de Vries et al. 2012).

Receptor-binding patterns of the H1N1pdm09 viruses were similar to that of swine triple-reassortant H1N1 viruses, with preferential binding to α-2,6-linked SA and less binding to the α-2,3-linked SA, suggesting that no major change in receptor-binding specificity was required for the pandemic virus to acquire human-like characteristics (Childs et al. 2009) and underscored the similarities between human and swine influenza infection. However, swine-adapted influenza viruses failed to replicate efficiently in the human upper airways and bronchi, in contrast to H1N1pdm09 and seasonal human influenza viruses (Chan et al. 2011). This indicates that factors other than receptor-binding specificity contributed to the sustained human-to-human transmission of H1N1pdm09 viruses. Receptor-binding specificity also does not sufficiently explain the restriction of other swine-adapted viruses, such as H3N2v, from sustained infection and transmission in the human population. A factor that may contribute to the efficient transmission of the H1N1pdm09 is the M gene of Eurasian swine origin, because swine triple-reassortant viruses that possess this gene showed improved replication in human nasopharynx and bronchus in vitro (Chan et al. 2011). However, the incorporation of the 2009 pandemic M gene into the triple reassortant internal gene backbone of the H3N2v viruses alone did not confer human-to-human transmission in the 2011–2012.
Host-Specific Factors in Influenza A Virus Infection

Protection from influenza infection comprises both the innate and adaptive branches of the immune system. The innate immune response is critical in the early stages of a primary influenza virus infection, forming the first line of defense through the control of early viral replication by natural killer cells, alveolar macrophages, and dendritic cells, as well as the induction of virus-specific innate immune responses (McGill et al. 2009). It encompasses many components, including mucus and acute phase proteins. Chemokines and cytokines such as IL-1, IL-6, IL-12, and -IFN are elevated in influenza-infected patients, particularly in severe and fatal cases (Cox et al. 2004; La Gruta et al. 2007). Levels of IL-6 and IFN- are directly correlated with viral titer and illness severity in patients infected with IAV (Hayden et al. 1998). In pigs, proinflammatory cytokines such as IL-1, IL-6, IL-12, and IFN- , as well as IFN- , TNF- , and IL-10, were elevated after IAV infection (Khatti et al. 2010; Van Reeth et al. 1998). These proinflammatory cytokines were also correlated with the pathology of the infection (Van Reeth et al. 2002).

In adaptive immunity, a virus-specific humoral response, particularly to the surface proteins HA and NA, correlates with protection in human influenza infection (Potter and Oxford 1979), provided that the strains are homologous or antigenically similar (de Jong et al. 2000). In swine, neutralizing antibodies against the HA protein are also correlated to clinical protection (Bikour et al. 1996); however, mismatch between priming and challenge virus results in failure of protection and may also be associated with enhanced respiratory disease (Gauger et al. 2011). Similar immune response-associated enhancement has been observed for healthy middle-aged adults during the 2009 pandemic, associated with low avidity cross-reacting antibodies and complement activation (Monsalvo et al. 2011). Furthermore, mucosal or secretory IgAs are important for local protection and neutralization of virus in early infection, and are elevated after vaccination with live attenuated virus vaccines in human patients as well as in pigs (Loving et al. 2012; Moldoveanu et al. 1995). Local IgA correlates with resistance to infection and to illness after challenge of vaccinated patients (Clements et al. 1986). It is associated with protection in swine even in the absence of detectable systemic HI antibodies (Loving et al. 2012).

Cell-mediated immunity plays a critical role for infection resolution and clearance of influenza virus, either by CD4+ T-cell activation of B cells and subsequent antibody production or through CD8+ T-cell-mediated lysis of infected cells. Because CD8+ T cells are directed against more conserved epitopes, they have been shown to be essential to mediate heterosubtypic immunity in influenza infection (Heinen et al. 2001; Kreijtz et al. 2007). However, in a recent study, CD4+ memory T cells, and not CD8+ cells, were associated with less severe symptoms and lower viral shedding in patients challenged with H3N2 and H1N1 viruses (Wilkinson et al. 2012). In swine, CD4+/CD8+ double-positive T cells possess memory properties (Zuckermann 1999) and are increased in the lung, tracheobronchial lymph nodes, and tonsils of IAV-vaccinated infected pigs (Khatti et al. 2010). Notably, most available data for influenza immunology have been obtained through the use of the murine model; however, as stated previously, mice are not natural hosts and the model is far from ideal. The similarities between the immune responses of infected or vaccinated swine and humans described above suggest the pig is an excellent candidate for modeling the human immune response to flu.

Transmission of Influenza A Viruses

Three different routes can spread influenza viruses from individual to individual: direct contact with infected individuals; contact with contaminated fomites; and inhalation of aerosols containing virus (Carrat et al. 2008; Pica and Bouvier 2012). Factors related to host specificity are also related to viral transmission in influenza infection. For airborne transmission in humans, influenza viruses require human rather than avian receptor-binding preference (Herfst et al. 2012). Some individuals show higher efficiency to transmit the virus (Stein 2011), and epidemiological records suggest that children and immunocompromised individuals appear to transmit more efficiently and for longer periods (Thangavel and Bouvier 2014). IAVs are most frequently isolated from weaned juvenile piglets from 4 to 8 weeks of age (Takemae et al. 2011); however, this might be due to epidemiological and production factors, in addition to increased transmission efficiency in young pigs. Similar to other experimental model species, such as guinea pigs and ferrets (Herlecher et al. 2001; Lowen et al. 2014), influenza viruses can efficiently transmit by aerosol in pigs (Kitikoon et al. 2012), and they are natural hosts. Thus, this species can also be used to study viral and host factors related to the transmission of human viruses.
Conclusion

Several animal species have been used in influenza virus research, each with specific advantages and disadvantages. The porcine model has been successfully used for research of many human diseases, including influenza, mainly for vaccine efficacy and trial studies. Pigs are natural hosts of influenza viruses and have a crucial role in the emergence and epidemiology of novel influenza viruses. More importantly, swine are genetically and physiologically closely related to humans, and show similar clinical signs and pathology upon IAV infection. Pigs should be considered a suitable and valuable model for influenza A virus infection, in regards to pathogenesis, transmission, and immune response to infection or vaccines.

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