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Up to new tricks – A review of cross-species transmission of influenza A viruses

Gabriele A. Landolt[1]* and Christopher W. Olsen[2]

[1]*Department of Clinical Sciences, Colorado State University, 300 West Drake Road, Fort Collins, CO 80523, USA and* [2]*Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin-Madison, 2015 Linden Drive, Madison, WI 53706, USA*

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Abstract

Influenza is a highly contagious disease that has burdened both humans and animals since ancient times. In humans, the most dramatic consequences of influenza are associated with periodically occurring pandemics. Pandemics require the emergence of an antigenically novel virus to which the majority of the population lacks protective immunity. Historically, influenza A viruses from animals have contributed to the generation of human pandemic viruses and they may do so again in the future. It is, therefore, critical to understand the epidemiological and molecular mechanisms that allow influenza A viruses to cross species barriers. This review summarizes the current knowledge of influenza ecology, and the viral factors that are thought to determine influenza A virus species specificity.

Keywords: Influenza A virus, cross-species transmission, ecology, species-specificity

Introduction

Influenza is a highly contagious disease that represents one of the most serious health and economic threats to humans and animals worldwide. In order to understand the epidemiology of influenza, it is critical to recognize that influenza A viruses infect a wide variety of species. Moreover, the viruses exhibit only partial restriction of their host range such that viruses from one species can occasionally transmit to infect another species (Webster *et al*., 1992; Webby and Webster, 2001). Historically, only a limited number of subtypes of influenza viruses have been associated with widespread infection of mammals (Webster *et al*., 1992; Alexander and Brown, 2000). However, viruses of all 16 hemagglutinin (HA) and nine neuraminidase (NA) subtypes have been recovered from wild waterfowl and seabirds (Webster *et al*., 1992; Webby and Webster, 2001). As such, waterfowl provide a vast global reservoir of influenza viruses in nature from which novel viruses can emerge to infect mammalian species (Webster *et al*., 1992; Webby and Webster, 2001). Undoubtedly, the most prominent examples of direct transmission of avian viruses to mammalian species are the recent infections of humans and cats with the highly pathogenic avian H5N1 viruses (de Jong *et al*., 1997; Claas *et al*., 1998b; Kuiken *et al*., 2004; Webster *et al*., 2005). Yet, while these examples clearly demonstrate that cross-species transmission of viruses can occur, it has long been recognized that barriers exist that limit transmission of influenza viruses among species (Webster *et al*., 1992; Webby and Webster, 2001).

In general, the ability of any given virus to cross from one species to another is dependent on epidemiological factors as well as host and viral factors. For example, some viruses are prevented from entering a new host species simply by the absence of the appropriate receptor (Morse, 1997). Other viruses are able to enter the host cell, yet, they are unable to complete their replication cycle (Morse, 1997). Many viruses that have demonstrated the ability to transmit between species that contain RNA genomes. As viral RNA polymerases lack proofreading functions, RNA viruses generally demonstrate high mutation rates (for influenza A viruses the mutation rate is estimated at one point mutation/1.5×10^5 nucleotides) (Buonagurio *et al*., 1986), with consequent potential for rapid evolution. As this mutation rate is sufficiently high to yield one or more point mutations in each progeny

*Corresponding author. E-mail: landoltg@colostate.edu

viral genome per round of replication, viral stocks often represent a population of genomes, a 'quasispecies' (Eigen and Schuster, 1977), rather than a homogenous population (Morse, 1997). This genetic diversity allows plasticity within the viral population, for example, for adaptation to a new environment such as a new host species. Despite this, many viruses show remarkable genetic stability in their natural hosts. In waterfowl, influenza viruses are generally highly host-adapted, as evidenced by low evolutionary rates ('evolutionary stasis') (Gammelin *et al.*, 1990; Gorman *et al.*, 1992; Webster *et al.*, 1992; Webby and Webster, 2001).

As a general rule, upon introduction into a new environment (i.e. a new host species), selection of mutants that are most 'fit' (i.e. replicate most efficiently in the new environment) will be selected from within the population of virus genomes. The selective pressure may affect regions in the virus genome that convey a replication advantage, control species specificity, or correspond to antigenic sites (Morse, 1997). The genetic diversity within a virus population is determined by the balance between the emergence of new mutants and the extinction of circulating variants through competition (Ferguson *et al.*, 2003). For human influenza viruses, selection by the host immune system is thought to be the driving force in the production of influenza genetic diversity. As protection conferred by influenza-specific immunoglobulins decreases with increasing genetic divergence of the HA, cross-protection tends to decrease as the antigenic divergence between two strains increases (Ferguson *et al.*, 2003). Theoretically, this should result in the selection of antigenically novel strains and subsequent exponential growth of influenza virus diversity. Yet, at any given time, human influenza virus strains demonstrate a surprisingly limited genetic diversity (Ferguson *et al.*, 2003). Although recent results indicate that multiple lineages of virus strains are represented in the influenza virus population (Ghedin *et al.*, 2005), human influenza virus evolution seems to be characterized by the continuous replacement of circulating strains (Webster *et al.*, 1992; Webby and Webster, 2001). In fact, phylogenetic analyses suggest that genetic evolution of human influenza viruses follows a multi-strain population dynamic, in which 95% of strains are maintained in the population for less than one year. Only approximately 1% of influenza virus strains will become established in the human population on a global scale (Fitch *et al.*, 1997; Ferguson *et al.*, 2003). More recent results by Wolf and colleagues (Wolf *et al.*, 2006) indicate that evolution of human influenza viruses may not be linear, but rather occurs in periods of rapid fitness change (and displacement of old lineages with new dominant ones), followed by intervals of relative evolutionary stasis of the influenza virus genome. These periods of stasis are characterized by generally neutral sequence substitutions without apparent changes in the antigenic properties of the virus and, thus, only slow extinction of coexisting virus lineages (Wolf *et al.*, 2006). Regardless of the selection mechanisms involved, the subsequent step in virus emergence hinges on the virus's ability to maintain itself in the new population. This step requires efficient transmission of the virus among individuals of the new species and is dependent on viral factors (such as replication potential), population factors (such as host density), and host factors (such as immune status and response to the pathogen) (Morse, 1997).

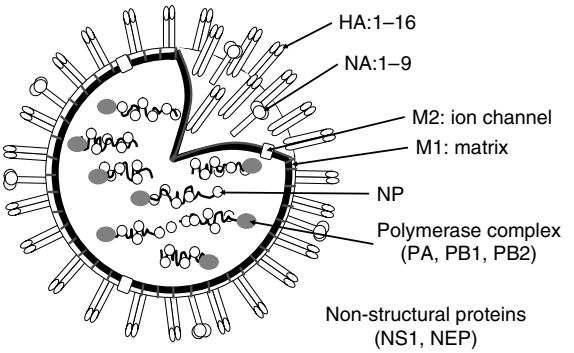

Fig. 1. Schematic diagram of structural components of influenza A virus. Three integral membrane proteins – HA, NA, and the ion channel protein (M2) – are embedded in the lipid envelope of the virion. The matrix protein (M1) underlies the lipid envelope. Associated with the viral RNA is the polymerase complex, consisting of PA, PB1, and PB2. The viral nucleoprotein (NP) encapsidates the viral RNA segments.

Given the plasticity of the virus genome, influenza fulfills the prerequisites of a virus with emerging disease potential (Webster *et al.*, 1993). It is highly likely that sometime in the near future a 'new' influenza A virus, be it one of the H5N1 viruses currently circulating in the wild bird population in large parts of Asia or a different virus, will be able to emerge from its animal reservoir to cause widespread disease in mammalian species. The impact of influenza in humans and animals, whether measured by morbidity, mortality or economic losses, is substantial. It is, therefore, essential to understand the precise epidemiological and molecular mechanisms that allow these viruses to jump species barriers and establish themselves in new populations. This review focuses on transmission of viruses between species, discussing both direct transmission of viruses from aquatic birds to mammals and virus transmission between mammalian species. This also includes a discussion of the molecular factors that are thought to affect influenza virus species specificity.

Etiology

Influenza viruses are members of the family *Orthomyxoviridae* and are enveloped viruses with segmented, single-stranded, negative-sense RNA genomes (schematically depicted in Fig. 1). The *Orthomyxoviridae* comprise

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five genera; influenza A, B, and C viruses, thogotovirus, and isavirus (Wright and Webster, 2006). Influenza A viruses are distinguished from types B and C based on genetic and antigenic differences in their nucleoprotein (NP) and matrix (M) proteins. In addition, influenza A and B viruses contain eight separate segments of single-stranded RNA, whereas influenza C viruses possess only seven. In contrast to influenza A viruses that infect a wide variety of animals, influenza B viruses are primarily human pathogens. Influenza C viruses have most commonly been isolated from humans, but these viruses can also infect pigs and dogs (Ohwada *et al.*, 1987; Manuguerra *et al.*, 1993).

Influenza A virions possess a host-cell-derived lipid envelope, are 80–120 nm in diameter, and, if propagated in eggs or cell culture, have a fairly regular spherical appearance. In contrast, on initial isolation from humans or animals, influenza A viruses exhibit pleomorphism (Lamb and Krug, 2006). Embedded in the lipid envelope are the HA and NA, forming about 500 spikes radiating outward, and the integral M2 protein, which functions as an ion channel (Lamb and Krug, 2006). The HA serves as the viral receptor-binding protein and mediates fusion of the virus envelope with the host cell membrane (Wharton *et al.*, 1989; Skehel and Wiley, 2000). Each monomer of the trimeric HA protein consists of a globular head, made up exclusively of HA1, and a stalk, which consists of all of HA2 and parts of HA1 (Lamb and Krug, 2006). The globular head portion contains the receptor-binding site, which is comprised of an antibody-inaccessible pocket. Thus protected from immunological pressure, the amino acid residues located in the receptor-binding site are largely conserved among subtypes (Wilson *et al.*, 1981; Wharton *et al.*, 1989; Skehel and Wiley, 2000). The HA is the major target of the host humoral immune response. There are five antigenic regions that cover much of the surface of the globular head portion of the molecule. Host immune pressure is the driving force in selecting mutant viruses with amino acid substitutions in these antigenic sites, a process also referred to as 'antigenic drift' (Fig. 2) (Wharton *et al.*, 1989; Lamb and Krug, 2006).

The NA is a type II integral membrane protein and is the second large glycoprotein embedded in the influenza virus envelope (Varghese *et al.*, 1983; Colman *et al.*, 1987). The NA is responsible for the cleavage of the α-ketosidic linkage between a sialic acid (SA) molecule and an adjacent sugar residue (Gottschalk, 1957). Biologically, the protein assists in the release of budding virus particles by removing SA residues from the viral glycoproteins as well as the infected cell (Palese *et al.*, 1974; Bucher and Palese, 1975; Air and Laver, 1989). More recent data also indicate that the NA plays an essential role in virus invasion of the respiratory tract by catalyzing the cleavage of the α-ketosidic linkage between the terminal SA and the adjacent sugar residue in mucus (Castrucci and Kawaoka, 1993; Matrosovich *et al.*, 2004b).

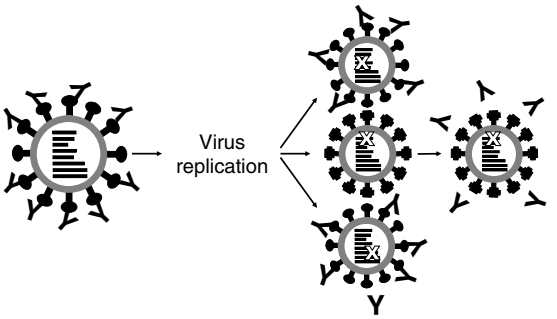

Fig. 2. Schematic diagram illustrating antigenic drift. The influenza A virus RNA polymerase lacks proofreading function. The mutation rate of the influenza virus genome is sufficiently high to yield one or more point mutations (represented by the 'X') in each progeny viral genome per round of replication. Host immune pressure is the driving force in the selection of mutants with amino acid substitutions in antigenic sites on the HA and NA envelope glycoproteins.

Like the HA, the NA contains antigenic determinants and undergoes substantial antigenic variation in response to immune pressure (Wright and Webster, 2006).

The M2 protein, the third envelope glycoprotein present in the influenza virion, serves as an ion channel (Pinto *et al.*, 1992; Wang *et al.*, 1993; Holsinger *et al.*, 1994). The M2 ion channel is activated at low pH and allows hydrogen ions to enter the virion during uncoating. In addition, M2 modulates the pH of the Golgi apparatus, thus preventing premature conformational change of the HA protein prior to virus assembly (Hay, 1992; Cleverley *et al.*, 1997; Liu and Ye, 2002; Wright and Webster, 2006). The M1 protein is the most abundant protein present in the influenza virion. M1 lies beneath the lipid envelope, providing rigidity to the membrane that surrounds the eight ribonucleoprotein (RNP) complexes (Lamb and Krug, 2006). Each RNP complex consists of a single RNA segment, encapsidated by NP molecules, as well as the three polymerase proteins PA, PB1, and PB2 (Lamb and Krug, 2006; Noda *et al.*, 2006). The segmented nature of the influenza virus genome is a key feature of the influenza virus structure. In the event that cells are infected with two (or more) different viruses, exchange of RNA segments between the viruses allows the generation of progeny viruses containing a novel combination of genes ('genetic reassortment'). In theory, genetic reassortment could potentially lead to the creation of 254 new gene combinations from two parental viruses (Wright and Webster, 2006).

Influenza viruses encode two 'non-structural' (NS) proteins NS1 and NS2. While the NS2 or nuclear export protein (NEP) was originally thought to be non-structural, it has since been found to be a part of the influenza virion (Richardson and Akkina, 1991; Yasuda *et al.*, 1993). In contrast, although NS1 is abundantly present in infected cells during virus replication, the protein is not

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incorporated into progeny virions (Wright and Webster, 2006).

Impact of influenza A virus infections

The incidence of influenza A virus infection in the human population varies significantly from year to year and is dependent on the attack rate, virulence of the circulating strain, and on the degree of immunity of individuals in the population (Alexander and Brown, 2000). Nevertheless, the impact of yearly human influenza epidemics is substantial, resulting in an average of 114,000 hospitalizations, 36,000 deaths and up to $10 billion in medical costs and lost income in the United States alone (Klimov *et al.*, 1999; Cox and Subbarao, 2000; Bridges *et al.*, 2002a, 2003; Thompson *et al.*, 2003). In temperate climates, influenza epidemics typically occur in the winter months. In contrast, in the tropics the disease can occur year round (Cox and Subbarao, 2000). Due to antigenic drift, the antigenicity of circulating influenza viruses is constantly changing. This allows the drift variants to infect individuals that were immune to previously circulating influenza strains (Cox and Subbarao, 2000; Subbarao *et al.*, 2006). Therefore, the influenza viruses included in human vaccines have to be reviewed and potentially updated each year to keep pace with antigenic drift (Cox and Subbarao, 2000; Subbarao *et al.*, 2006). Influenza surveillance is coordinated by the World Health Organization's (WHO) global influenza surveillance program.

The most dramatic consequences of influenza are associated with the periodic occurrence of influenza pandemics. Influenza pandemics are defined as global outbreaks of disease due to the emergence of viruses that contain envelope glycoproteins to which the human population is immunologically naïve (Horimoto and Kawaoka, 2001). In modern times, pandemics occurred in 1918 ('Spanish flu', H1N1), 1957 ('Asian flu', H2N2), 1968 ('Hong Kong flu', H3N2), and on a much more limited scale in 1977 ('Russian flu', H1N1) (Webster *et al.*, 1992; Cox and Subbarao, 2000; Horimoto and Kawaoka, 2001; Wright and Webster, 2006). The devastation that influenza pandemics can cause was clearly demonstrated by the 1918 'Spanish flu' pandemic that killed an estimated 40–50 million people worldwide (Crosby, 1989; Taubenberger *et al.*, 2000; Potter, 2001; Taubenberger, 2003). Projections of the impact of the next influenza pandemic in the United States alone include 89,000–207,000 deaths, 314,000–734,000 hospitalizations, and up to $166 billion in direct costs (Meltzer *et al.*, 1999; Ferguson, 2006; Layne, 2006; Maldin and Criss, 2006).

While 'fowl plague', the disease caused by highly pathogenic avian influenza (HPAI) viruses in poultry, has been recognized since the late 18th century, the close relationship between the infectious agents causing 'fowl plague' and mammalian influenza was not demonstrated until 1955 (Webster *et al.*, 1992; Alexander and Brown, 2000). HPAI viruses are restricted to H5 and H7 subtypes and clinical signs associated with infection in birds vary according to the species, age, virus strain, and environmental factors involved (Webster *et al.*, 1992; Alexander and Brown, 2000; Swayne and Suarez, 2000; Mutinelli *et al.*, 2003; Jones and Swayne, 2004; Ramirez *et al.*, 2005; Isoda *et al.*, 2006). Typically, HPAI viruses are not maintained in the wild waterfowl population, but are thought to appear by introduction of H5 and H7 low-pathogenicity avian influenza viruses (LPAI) in land-based poultry and subsequent mutation to HPAI in these birds (Rohm *et al.*, 1995; Subbarao *et al.*, 2006). Clinical signs associated with HPAI infection may include cessation of egg laying, high fever, subcutaneous and internal hemorrhages, necrosis of the comb and wattles, edema of the head and neck, and cyanosis of the unfeathered skin (Alexander and Brown, 2000; Swayne and Suarez, 2000; Ramirez *et al.*, 2005; Isoda *et al.*, 2006). In contrast to LPAI viruses, which cause only mild respiratory disease and minimal to no mortality, HPAI viruses spread systemically and infection often rapidly results in death (Swayne and Suarez, 2000). Therefore, outbreaks of HPAI often carry severe consequences for animal health as well as the economy of the region where they occur. For example, the outbreak of HPAI in Pennsylvania in the early 1980s resulted in 17 million culled birds, including chickens, turkeys, chukar partridges, and guinea fowl, and cost more than 60 million dollars to eradicate (Acland *et al.*, 1984; Subbarao *et al.*, 2006). The outbreak of HPAI H5N1 virus in Hong Kong in 1997 resulted in the culling of 1.4 million chickens and other in-contact birds (Subbarao *et al.*, 2006). Lastly, hundreds of millions of domestic poultry have died or have been culled to prevent the spread of the avian H5N1 virus and the economic impact the disease has had on affected countries is estimated to exceed 10 billion dollars (Kilpatrick *et al.*, 2006). In the past, most outbreaks of HPAI were caused by a single lineage of HPAI virus. Moreover, as a result of extensive eradication programs, the virus was eliminated from the domestic bird population in less than a year (Subbarao *et al.*, 2006). The Asian H5N1 outbreaks appear to follow a different pattern and have been characterized by the detection of multiple reassortant viruses in domestic poultry (Guan *et al.*, 2003). Apart from the substantial socioeconomic implications of HPAI infection in poultry, transmission of H5N1 and H7N7 viruses to humans have clearly demonstrated the significant zoonotic threat these viruses pose (de Jong *et al.*, 1997; Claas *et al.*, 1998b; Fouchier *et al.*, 2004; Webster *et al.*, 2005). By February 2007, the re-emergence of H5N1 HPAI in Asia and subsequent spread of the viruses to Europe and Africa, has resulted in 274 human cases, including 167 deaths (www.who.int/csr/disease/avian_influenza/en).

Although a recent study demonstrated the potential of low-pathogenic avian influenza virus to cause clinical disease in wild birds (van Gils *et al.*, 2007), influenza

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infection in waterfowl typically is thought to result only in subclinical infection in these animals (Webster *et al.*, 1978, 1992). The viruses preferentially replicate in the duck intestinal tract and are shed in high concentrations in the feces, thereby contaminating the lakes and ponds the birds visit (Halvorson *et al.*, 1983; Webster *et al.*, 1992; Laver *et al.*, 2000). As viruses of all 16 HA and nine NA subtypes are maintained in aquatic birds, particularly in migrating waterfowl, these birds represent a vast global reservoir of influenza (Halvorson *et al.*, 1983; Webster *et al.*, 1992; Laver *et al.*, 2000). Indeed, viruses of avian origin have been the source of outbreaks of influenza in mammals, such as seals, whales, mink, pigs, and horses (Geraci *et al.*, 1982; Hinshaw *et al.*, 1984, 1986; Klingeborn *et al.*, 1985; Chambers *et al.*, 1989; Guo *et al.*, 1992; Callan *et al.*, 1995; Shortridge *et al.*, 1995; Guan *et al.*, 1996; Brown *et al.*, 1997; Karasin *et al.*, 2000a).

Swine influenza, first clinically recognized in pigs during the late summer and fall of 1918 (Koen, 1919), has remained of substantial importance to the swine industry throughout the world (Webster *et al.*, 1992; Alexander and Brown, 2000; Olsen, 2002). Infection of pigs can pose serious economic consequences because of the prolonged time needed for affected pigs to reach slaughter weight (Janke, 1998). Clinical signs of influenza in pigs are similar to those observed in humans, and infections are manifested as outbreaks of acute respiratory disease characterized by fever, inactivity, decreased food intake, coughing, sneezing, and nasal discharge (McQueen *et al.*, 1968; Alexander and Brown, 2000; Kothalawala *et al.*, 2006; Subbarao *et al.*, 2006). In addition to the epizootic form of disease, influenza viruses are part of the porcine respiratory disease complex, acting in concert with other swine respiratory pathogens such as *Mycoplasma hyopneumoniae*, porcine reproductive and respiratory syndrome virus (PRRSV), and bacterial agents of pneumonia (Thacker *et al.*, 2001).

Since first diagnosed during an epidemic of respiratory disease in Eastern Europe in 1956 (Sovinova *et al.*, 1958), outbreaks of equine influenza have occurred regularly throughout most of the world. The clinical signs observed are similar to those seen in pigs and humans and disease severity is dependent on immune status, infecting dose and virus strain (Wilson, 1993; Hannant and Mumford, 1996). In vaccinated animals, the disease is rarely fatal, but deaths have been reported during some epidemics, particularly in donkeys (Wilson, 1993; Alexander and Brown, 2000). Severe epidemics have occurred relatively recently in India (Uppal *et al.*, 1989), the People's Republic of China (Guo *et al.*, 1992; Shortridge *et al.*, 1995), and South Africa (Guthrie *et al.*, 1999). In developed countries, equine influenza infections can largely be managed by vaccination and by resting of affected animals. In many other parts of the world, however, horses, donkeys and mules remain as principal working animals and influenza virus outbreaks can have severe socioeconomic impacts (Shortridge *et al.*, 1995).

Additional animal species from which influenza A viruses have been isolated include seals, mink, whales, feral and domestic cats, and dogs. In 1979–1980, harbor seals populating the northeastern coast of the United States died of respiratory disease, characterized by severe pulmonary consolidation. Influenza viruses, subtyped as H7N7, were demonstrated in the lungs and brains of the affected animals (Geraci *et al.*, 1982). Additional isolates from seals have included H3N3 and H4N6 influenza viruses (Hinshaw *et al.*, 1984; Callan *et al.*, 1995). Viruses of H13N2, H13N9, and H1N3 subtypes have been detected in the lungs of whales (Lvov *et al.*, 1978; Hinshaw *et al.*, 1986; Chambers *et al.*, 1989) and avian origin H10N4 viruses, causing systemic infection and disease, were isolated from farm-raised mink (Klingeborn *et al.*, 1985). Since 2004, infections of exotic and domestic cats with H5N1 HPAI viruses were documented on multiple occasions in Asia, the Middle East, and Europe (Kuiken *et al.*, 2004, 2006; Rimmelzwaan *et al.*, 2006; Songsermn *et al.*, 2006a; Yingst *et al.*, 2006; Leschnik *et al.*, 2007), of dogs in Thailand (Butler, 2006; Songsermn *et al.*, 2006b), and of a stone marten in Germany (www.who.int/csr/con/2006_03_09a/en/index.html). Lastly, in the spring of 2004, an influenza virus was isolated from lung tissues of greyhound dogs that had died from hemorrhagic pneumonia (Crawford *et al.*, 2005). Sequence analysis of the viral genome revealed that the canine isolate was closely related to and had evolved from a contemporary equine H3N8 virus (Peek *et al.*, 2004; Crawford *et al.*, 2005). Since then, canine influenza viruses have spread across large parts of the country and appear to have established themselves in the dog population of the United States (Crawford *et al.*, 2005).

Influenza virus ecology

The avian reservoir

Influenza pandemics are precipitated by an 'antigenic shift', which describes the replacement of the predominantly circulating influenza virus subtype with a novel HA subtype, to which the human population has not recently been exposed (Fig. 3) (Webster *et al.*, 1992; Wright and Webster, 2006). This novel virus can then evade immune surveillance and replicate largely unimpeded in the immunologically naïve population. Historically, only a limited number of subtypes of influenza viruses have been associated with infection of mammals. For example, in humans only viruses of H1, H2, H3, N1, and N2 subtypes have circulated widely in the population (Webster *et al.*, 1992; Alexander and Brown, 2000), in horses influenza infections have been largely restricted to viruses of H7N7 and H3N8 subtypes (Webster, 1993; Wilson, 1993; Alexander and Brown, 2000), and only H1, H3, N1, and N2 subtypes have been consistently isolated

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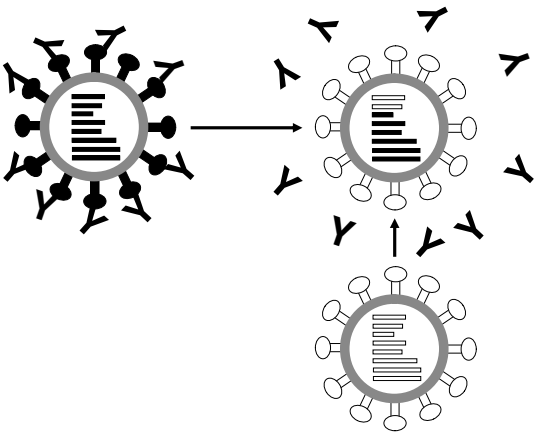

Fig. 3. Schematic diagram illustrating genetic reassortment. In the event that cells are infected with two (or more) distinct influenza viruses, the exchange of RNA gene segments between viruses allows the generation of progeny viruses containing novel combinations of genes. If such a reassortment event results in the introduction of a novel HA subtype, the new virus can escape neutralizing antibodies ('antigenic shift').

from pigs (Webster *et al.*, 1992; Olsen, 2002). The most widely accepted theory of how pandemic viruses emerge is that a virus with a novel subtype is introduced into the human population through transfer from the avian reservoir (Fig. 4), with or without genetic reassortment (Webster *et al.*, 1992, 1993; Horimoto and Kawaoka, 2001; Webby and Webster, 2001). This theory is supported by phylogenetic studies demonstrating that the 'Spanish flu' pandemic was caused by a virus that derived all its genes from an avian virus (Tumpey *et al.*, 2005), as well as the finding that the pandemic strains of 1957 and 1968 arose from genetic reassortment of contemporary human and avian influenza viruses (Gething *et al.*, 1980; Fang *et al.*, 1981; Kawaoka *et al.*, 1989). Several other findings highlight the importance of the avian reservoir. For example, there exists ample genetic evidence that viruses from aquatic birds were the ancestral precursors of all contemporary influenza virus lineages present in other species (Gammelin *et al.*, 1990; Gorman *et al.*, 1991; Webster *et al.*, 1992; Webster, 1998). In addition, direct transmission of an avian virus to horses resulted in the severe equine influenza epidemic that occurred in the Jilin and Heilongjiang Provinces in the northeast of the People's Republic of China in 1989 (Guo *et al.*, 1992). Lastly, there have been several well-documented occasions on which direct avian-to-swine transmissions of viruses have occurred (see below).

Yet, despite these examples, evidence also supports the existence of barriers that limit the transmission of influenza viruses from birds to mammals. For instance, prior to 1997 there were only three reports of human infections with avian influenza viruses (Campbell *et al.*, 1970; Taylor and Turner, 1977; Webster *et al.*, 1981). Although direct avian-to-human transmission of H5N1, H9N2, and H7N7 viruses have been described since then (de Jong *et al.*, 1997; Claas *et al.*, 1998a; Lin *et al.*, 2000; Bridges *et al.*, 2002b; Hatta and Kawaoka, 2002; Uyeki *et al.*, 2002; Katz, 2003; Fouchier *et al.*, 2004; Webster *et al.*, 2005), these avian viruses still appear not to have developed the ability to transmit efficiently from person to person [examples of suspected, limited human-to-human spread of H5N1 virus notwithstanding (Gilsdorf *et al.*, 2006; Kandun *et al.*, 2006)]. Yet, the ability to transmit efficiently among humans is considered to be one of the chief prerequisites for pandemic emergence of an influenza virus (de Jong *et al.*, 1997; Cox and Subbarao, 2000; Taubenberger and Morens, 2006).

In general, avian influenza viruses do not replicate well in humans and non-human primates, and vice versa, human viruses typically do not replicate well in birds (Hinshaw *et al.*, 1978, 1983; Webster *et al.*, 1978; Murphy *et al.*, 1982; Snyder *et al.*, 1987; Beare and Webster, 1991). Given this limited capacity for direct avian-to-human transmission, it is debatable whether the creation of pandemic viruses rests solely in either species. Rather, it is hypothesized that the emergence of an avian virus with pandemic potential requires prior adaptation in an intermediate host. Viral adaptation at the molecular level would then result in an avian-lineage virus with the ability to spread efficiently among humans (Scholtissek *et al.*, 1983; Scholtissek and Naylor, 1988; Scholtissek, 1990; Webster *et al.*, 1992; Brown, 2000b; Ito, 2000).

The role of intermediate hosts in the creation of pandemic viruses

Pigs have been suggested to support two processes that can lead to the development of influenza viruses with pandemic potential: adaptation and genetic reassortment. As avian viruses of virtually all HA subtypes (H1–H13) were able to infect and replicate in pigs under experimental conditions, these animals have been postulated as the logical intermediate host in which adaptation of avian viruses may occur (Kida *et al.*, 1994). In support of these experimental results are several well-documented examples of direct avian-to-pig transmission of influenza viruses that have occurred under natural conditions. For example, in 1979 a wholly avian H1N1 influenza virus crossed the species barrier to infect pigs in Europe (Pensaert *et al.*, 1981). These avian-lineage viruses subsequently became established in the pig population throughout much of Europe (Pensaert *et al.*, 1981; Scholtissek *et al.*, 1983; Donatelli *et al.*, 1991; Schultz *et al.*, 1991; Brown *et al.*, 1997; Webby and Webster, 2001). Other examples of *in toto* transmission of avian viruses to pigs include the transmission of H1N1, H3N2, H5N1, and H9N2 viruses to pigs in China and Hong Kong (Kida *et al.*, 1988; Guan *et al.*, 1996; Peiris *et al.*, 2001; Xu *et al.*, 2004; Choi *et al.*, 2005), as well as infections

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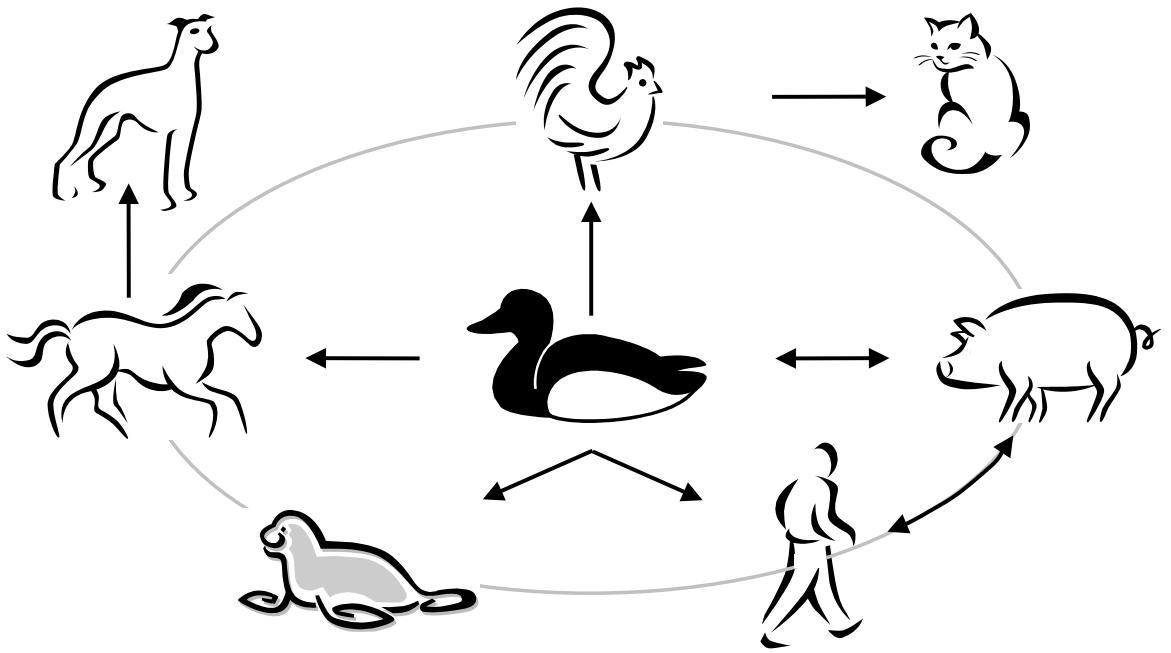

Fig. 4. Schematic representation of influenza A virus cross-species transmission. Research indicates that wild aquatic birds are the ancestral source of all influenza A viruses present in birds and mammals.

of pigs with H4N6, H1N1, and H3N3 viruses in Canada (Karasin *et al.*, 2000a, 2004).

Binding of influenza virus to its cellular receptor is determined by two properties: the SA species [e.g. *N*-acetylneuraminic (NeuAc) or *N*-glycolylneuraminic (NeuGc) acid] involved, as well as the NeuAc or NeuGc linkage to galactose residues (e.g. α2,6Gal or α2,3Gal) on the cell membrane. While avian viruses prefer binding to SA with α2,3Gal linkages in NeuGc or NeuAc forms, human lineage viruses preferentially bind to NeuAcα2,6Gal-linked receptors (Suzuki, 1994; Ito, 2000; Ito and Kawaoka, 2000; Suzuki *et al.*, 2000; Varki, 2001). This is consistent with the fact that avian intestinal cells primarily express α2,3-linked receptors, whereas human tracheal epithelial cells predominantly express α2,6-linked receptors (Rogers and Paulson, 1983; Suzuki, 1994; Gambaryan *et al.*, 1997; Matrosovich *et al.*, 1997; Vines *et al.*, 1998; Ito, 2000). Yet, a study by Gambaryan and colleagues (Gambaryan *et al.*, 2002) demonstrated that SAs expressed in chickens are not exclusively of α2,3 linkage, supporting the notion that these birds could act as a potential intermediate host for the transmission of influenza viruses from aquatic birds to humans. Moreover, Wan and Perez (2006) found that SAs expressed in the trachea of Japanese quail are of both α2,3 and α2,6 forms. Vice versa, the SAs expressed in the human airway are also not exclusively of α2,6 linkage. While the α2,6-linked sialyloligosaccharides are the predominant receptor type expressed on the respiratory epithelial cells of the human nasal passages and trachea, a recent study by Matrosovich and colleagues (Matrosovich *et al.*, 2004a) indicated that a subset of human tracheal respiratory epithelial cells also express the α2,3Gal-linked SAs. Moreover, Shinya and coworkers (Shinya *et al.*, 2006) found that non-ciliated cuboidal bronchiolar cells, as well as a substantial proportion of cells lining the alveolar walls (most likely alveolar type II cells) of the human lungs, also expressed SAα2,3Gal. The presence of SAα2,3Gal-bearing cells deep in the human respiratory tract supports the findings that viruses that have retained the avian-type receptor specificity can infect humans and cause lethal disease (Matrosovich *et al.*, 1999).

Nevertheless, efficient transmission of avian viruses among human beings requires the HA protein to adapt to preferentially bind to the human-type SAα2,6Gal receptors (Neumann and Kawaoka, 2006). As the respiratory epithelial cells of the porcine tracheal epithelium possess both SAα2,3Gal (NeuAc and NeuGc) as well as SAα2,6Gal receptors, pigs may serve as adaptation hosts in which the switch from avian-type to human-type receptor preference could occur (Couceiro *et al.*, 1993; Suzuki *et al.*, 1997; Ito *et al.*, 1998; Ito, 2000). For instance, an avian virus may initially infect pigs by employing SAα2,3Gal receptors. With continued replication in pigs, the virus may then adapt its receptor specificity to NeuAcα2,6Gal, thus providing a potential link from birds to humans (Ito *et al.*, 1998; Ito, 2000). This scenario is particularly attractive in light of the fact that adaptation of the HA receptor-binding preference was observed after introduction of the avian H1N1 influenza virus into pigs in Europe in 1979 (Rogers and D'Souza, 1989; Ito, 2000). Also, the subsequent recovery of these viruses from

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human patients in The Netherlands (Rimmelzwaan *et al.*, 2001) confirmed that these viruses had also become infectious for human beings.

Secondly, since pigs are also susceptible to infection with human lineage viruses (Kundin, 1970; Shortridge *et al.*, 1977; Hinshaw *et al.*, 1978; Nakajima *et al.*, 1982; Ottis *et al.*, 1982; Mancini *et al.*, 1985; Bean *et al.*, 1992; Shu *et al.*, 1994; Bikour *et al.*, 1995; Brown *et al.*, 1995; Nerome *et al.*, 1995; Karasin *et al.*, 2000c; Song *et al.*, 2003), these animals may serve as 'mixing vessel' hosts for genetic reassortment between human and avian viruses. According to this hypothesis, if two or more distinct influenza viruses co-infect a pig, the viruses can exchange RNA segments during replication, which can lead to the creation of new virus variants (Scholtissek, 1990). While there is no direct evidence that the reassortment events leading to the 1957 or 1968 pandemic viruses occurred in pigs, genetic reassortment between human-like H3N2 and avian-like H1N1 viruses has happened more recently among pigs in Europe (Castrucci *et al.*, 1993). The resulting reassortant viruses contained mammalian HA and NA surface glycoproteins, while maintaining the avian internal genes (Castrucci *et al.*, 1993; Brown *et al.*, 1998). And importantly, reassortant H3N2 and H1N2 viruses were subsequently also isolated from humans in Europe and Hong Kong (Claas *et al.*, 1994; Gregory *et al.*, 2001, 2002). Additional support for the 'mixing vessel' theory comes from the demonstration of 2-way (human/swine) and 3-way (avian/human/swine) reassortant viruses of H3N2, H1N2, H1N1, and H3N1 subtypes that have emerged in pigs since 1998 (Zhou *et al.*, 1999a; Karasin *et al.*, 2000b, c, 2002, 2006; Webby *et al.*, 2000, 2004; Choi *et al.*, 2002; Song *et al.*, 2003; Lekcharoensuk *et al.*, 2006; Ma *et al.*, 2006; Olsen *et al.*, 2006). In the United States, these reassortant viruses have subsequently spread widely within the country's swine population. However, equally important to note is the fact that persistent circulation of human influenza viruses in swine populations, though likely to facilitate the development of a pandemic virus in pigs through genetic reassortment, has occurred relatively rarely (Hinshaw *et al.*, 1978; Easterday, 1980; Ito, 2000). Consequently, it has been suggested that, as with maintenance of avian influenza viruses in the swine population, efficient infection of pigs with human influenza viruses may require mutational adaptation of the virus to the new swine host (Brown, 2000b; Lipatov *et al.*, 2004). In support of this notion are recent data demonstrating limited infectivity of a human virus following experimental infection of pigs (Landolt *et al.*, 2003, 2006).

For many years pigs have been considered the leading candidate for the intermediate host for avian-to-mammalian influenza virus adaptation; however, recent data suggest that terrestrial poultry, such as quail, chickens, and turkeys, may also play a central role in the emergence of viruses with pandemic potential. Surveillance in live bird markets in China, as well as experimental infection studies, demonstrated that land-based birds support replication of a variety of subtypes of avian influenza viruses (Liu *et al.*, 2003a, b; Perez *et al.*, 2003). More importantly, H5N1 and H9N2 viruses isolated from land-based poultry were found to have lower affinity for SAα2,3Gal than their respective counterparts isolated from aquatic birds (Matrosovich *et al.*, 1999, 2001; Saito *et al.*, 2001), suggesting that land-based poultry may serve as adaptation hosts for the conversion of SAα2,3Gal to SAα2,6Gal receptor preference (Matrosovich *et al.*, 2001; Perez *et al.*, 2003; Li *et al.*, 2004). This is consistent with the fact that both SAα2,3Gal and SAα2,6Gal receptors are expressed in trachea of these birds (Gambaryan *et al.*, 2002; Wan and Perez, 2006). The potential significance of terrestrial poultry as intermediate hosts is further highlighted by the finding that H7N3 viruses circulating since 2002 in the turkey population of Northern Italy were closely related to H7N3 strains isolated from wild ducks in 2001 (Capua *et al.*, 2002; Abe *et al.*, 2004; Campitelli *et al.*, 2004). Serological studies conducted in human beings with close contact with infected turkeys indicated that zoonotic transmission of the H7N3 viruses had also occurred (Puzelli *et al.*, 2005). Yet, despite these examples, recent data demonstrated that human and swine lineage influenza viruses were unable to replicate efficiently in terrestrial birds (Makarova *et al.*, 2003). Therefore, it appears that pigs remain the most likely domestic animal species in which genetic reassortment between avian and human viruses may occur.

Direct transmission between mammalian species

While the previous examples clearly illustrate the importance of the avian reservoir as a source of novel virus strains, influenza viruses of different genotypes and subtypes occasionally also can transmit between two mammalian species. The appearance of the 'Spanish flu' virus in 1918 might have involved this mechanism. Sequence data of the 1918 strain (Belshe, 2005; Tumpey *et al.*, 2005), as well as seroepidemiological studies of survivors of the 1918 pandemic, demonstrate that the pandemic 1918 H1N1 virus and the earliest swine H1N1 viruses were very closely related (Taubenberger *et al.*, 2000; Taubenberger and Morens, 2006). More recently, direct swine-to-human zoonotic transmission of influenza viruses has been documented on several occasions (Alexander and Brown, 2000; Myers *et al.*, 2006), including in North America (Hinshaw *et al.*, 1978; Dacso *et al.*, 1984; Patriarca *et al.*, 1984; Rota *et al.*, 1989; Wentworth *et al.*, 1994, 1997; Kimura *et al.*, 1998; Gaydos *et al.*, 2006; Olsen *et al.*, 2006), Europe (Claas *et al.*, 1994; Rimmelzwaan *et al.*, 2001; Gregory *et al.*, 2003), and Asia (Gregory *et al.*, 2001). Furthermore, serologic evidence collected from pig farm workers indicates that zoonotic infection may occur more often than the number of virus

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isolation reports suggests (Schnurrenberger *et al.*, 1970; Campitelli *et al.*, 1997; Olsen *et al.*, 2002; Ayora-Talavera *et al.*, 2005).

Apart from swine-to-human transmission of viruses, there exist only a handful of reports documenting zoonotic transmission of viruses involving other mammalian species. For instance, experimental infection of human volunteers with H3 equine-lineage viruses produced influenza-like illnesses associated with virus shedding and subsequent seroconversion (Couch *et al.*, 1969; Kasel and Couch, 1969). Conversely, occasional human-to-equine transmission of H1N1, H2N2, and H3N2 viruses has been reported (Tumova, 1980; Heilman and La Montagne, 1990) and experimental infection of horses with human H3N2 viruses demonstrated their susceptibility to infection with human viruses (Kasel and Couch, 1969). However, there is no evidence that horse-to-human or human-to-horse transmission routinely occurs under natural conditions. Lastly, data from serosurveillance and experimental challenge studies indicate that human-lineage viruses occasionally cross the species barrier to infect dogs (Ado and Titova, 1959; Nikitin *et al.*, 1972; Paniker and Nair, 1972; Bibrack, 1975; Bibrack *et al.*, 1975; Chang *et al.*, 1976; Houser and Heuschele, 1980). However, while these results indicate that dogs are susceptible to infection with human influenza viruses, infection did not result in clinical disease (Todd and Cohen, 1968; Bibrack, 1975; Bibrack *et al.*, 1975; Chang *et al.*, 1976; Houser and Heuschele, 1980) and these viruses did not spread efficiently among dogs (Nikitin *et al.*, 1972). In contrast, recent infections of dogs with an equine H3N8 virus have been associated with clinical signs of respiratory illness (including fatal hemorrhagic pneumonias), and recovery of virus from dogs from across the country, as well as serological evidence, indicate the spread and apparent maintenance of the virus within the canine population of the United States (Crawford *et al.*, 2005).

Molecular determinants of species specificity

As the preceding paragraphs demonstrate, cross-species transmissions of influenza A viruses occur relatively frequently. Yet, in many instances, these transmission events tend to be self-limiting and the newly introduced viruses are only rarely maintained in the new host species (Webster *et al.*, 1992). It has long been recognized that influenza A viruses exhibit partial restriction of their host range. Moreover, a number of subtypes of influenza viruses are rarely detected in animals other than their typical host (Webster *et al.*, 1992; Webby and Webster, 2001), suggesting that specific subtypes differ in their ability to cross the species barrier (Brown, 2000a). While the viral and host factors that determine influenza virus host range are only incompletely understood, evidence has accumulated over the years indicating potential contributions by all eight gene segments (Scholtissek *et al.*, 1985; Tian *et al.*, 1985; Snyder *et al.*, 1987, 1990; Murphy *et al.*, 1989; Webster *et al.*, 1992; Castrucci and Kawaoka, 1993; Subbarao *et al.*, 1993; Horimoto and Kawaoka, 2001; Hatta *et al.*, 2002; Li *et al.*, 2005; Dalton *et al.*, 2006; Neumann and Kawaoka, 2006). Examination of the contributions of individual viral proteins to host range restriction is complicated by a number of factors. For one, mutations often appear not in just one, but in multiple gene segments during the process of virus adaptation to a new host species. For example, sequence analysis of six human H5N1 isolates revealed that the viruses had acquired a variety of amino acid substitutions, affecting not only their HA, but also the internal proteins (PB2, PB1, PA, NP, M, and NS) (Suarez *et al.*, 1998; Bender *et al.*, 1999; Hiromoto *et al.*, 2000). As some of the substitutions in NP, PB2, and M2 occurred in sites previously defined as potential species-specific signatures of human versus avian H5N1 isolates, these mutations may indeed reflect adaptation of the virus to the new host species (Zhou *et al.*, 1999b; Hiromoto *et al.*, 2000). However, some of the other substitutions could also have been introduced in response to host immunological pressure or they may simply represent spurious mutations (Zhou *et al.*, 1999b; Hiromoto *et al.*, 2000). To complicate matters further, specific constellations of gene segments may be involved in controlling influenza virus species specificity. This notion is supported by the finding that during the reassortment events that led to the creation of the 1957 and the 1968 pandemic strains, both viruses acquired the avian HA and PB1 genes (as well as the avian NA in 1957) (Kawaoka *et al.*, 1989). Yet, despite such complexities, several genes appear to play dominant roles in controlling influenza host range, and the following paragraphs will review the current knowledge of the molecular determinants of influenza host range.

HA

Due to its role as the viral receptor-binding protein, many investigators have focused their attention on the HA as the primary determinant of host range, and over the years a large body of evidence has accumulated indicating that the HA is, in fact, a key player in influenza virus species specificity (Chambers *et al.*, 1989; Aytay and Schulze, 1991; Inkster *et al.*, 1993; Vines *et al.*, 1998; Bender *et al.*, 1999; Ito *et al.*, 1999; Suzuki *et al.*, 2000; Hatta *et al.*, 2002; Romanova *et al.*, 2003; Medeiros *et al.*, 2004). As previously discussed, avian influenza viruses bind preferentially to SAα2,3Gal, while human lineage influenza viruses prefer α2,6-linked SA receptors. Analysis of the three-dimensional structure of the H3 HA from human influenza viruses has revealed that the binding site that accommodates the SA receptor is a shallow pocket, formed by amino acid residues that are fairly highly conserved among virtually all subtypes and strains

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of influenza A viruses (Wright and Webster, 2006). Research has demonstrated that subtle differences in the amino acid residues that form the binding site can result in alterations of the receptor-binding properties of the HA molecule. For example, analysis of the HA gene of the 1968 pandemic strain by Bean and coworkers (Bean *et al.*, 1992) revealed that fewer than six amino acid residues in the HA of the 1968 Hong Kong pandemic virus were altered in the process of avian-to-human transmission. All of the mutations occurred in the globular head portion of the HA and included amino acid substitutions at positions 62, 144, 193, and 226 (Bean *et al.*, 1992). The mutation affecting residue 226 was found to be of particular interest in regard to receptor-binding specificity. Leucine (Leu)-226 was found to confer SAα2,6Gal specificity in human H2 and H3, but not H1, viruses (Matrosovich *et al.*, 2000; Skehel and Wiley, 2000), whereas glutamine (Gln) at position 226 correlates with SAα2,3Gal preference in avian and equine H3 viruses (Naeve *et al.*, 1984; Vines *et al.*, 1998). With the exception of a few early isolates, human viruses with Leu at position 226 typically contain serine (Ser) at residue 228, while glycine (Gly)-228 is associated with Gln-226 in avian viruses (Naeve *et al.*, 1984; Vines *et al.*, 1998). While there exists less evidence for its role in receptor specificity compared to residue 226, in most human H3 viruses, Ser at residue 193 is associated with SAα2,6Gal specificity, while asparagine (Asn) or lysine (Lys)-193 is associated with SAα2,3Gal specificity in avian and equine H3 viruses (Medeiros *et al.*, 2004). Aspartic acid (Asp)-190 was found to determine SAα2,6Gal specificity in human and swine H1 isolates, whereas glutamic acid (Glu)-190 correlates with the avian-type receptor-binding preference (Gammelin *et al.*, 1990; Kobasa *et al.*, 2004; Stevens *et al.*, 2004). Finally, both single and combined mutations of the amino acid residues at position 182 (Asn to Lys) or position 192 (Gln to arginine) converted the receptor-binding specificity of avian H5N1 viruses to the human-type SAα2,6Gal receptor specificity (Yamada *et al.*, 2006).

In addition to the amino acid sequence of the HA molecule, receptor-binding specificity is also influenced by the number and position of N-linked oligosaccharides at or around the receptor-binding site (Deom *et al.*, 1986; Aytay and Schulze, 1991; Gunther *et al.*, 1993; Inkster *et al.*, 1993; Matrosovich *et al.*, 1997; Gambaryan *et al.*, 1998; Baigent and McCauley, 2001; Banks and Plowright, 2003; Abe *et al.*, 2004). Variation of glycosylation around the receptor-binding site can often be observed following adaptation of a virus to growth in a new host species or cell line. For example, adaptation of influenza viruses to growth in eggs (Robertson *et al.*, 1993; Banks and Plowright, 2003; Romanova *et al.*, 2003), in mice (Gitelman *et al.*, 1986), or in mammalian cell lines (Crecelius *et al.*, 1984; Gunther *et al.*, 1993; Robertson *et al.*, 1995; Romanova *et al.*, 2003), resulted in alterations in glycosylation patterns. Furthermore, glycosylation patterns of the HA may be directly associated with species specificity. This is illustrated by the fact that a glycosylation site at position 63, commonly found in H3 viruses of human origin, is absent in avian-lineage H3 viruses (Kida *et al.*, 1988). Moreover, research demonstrated that adaptation of the H1N1 human strain A/USSR/90/77 to mice resulted in the loss of glycosylation sites at either position 131 (Asn to Asp) alone or in combination with position 94 (Thr to Ala). Growth of the virus in a mammalian cell line [Madin Darby canine kidney (MDCK) cells] led to the selection of variants with a single mutation at position 131 (Asn to Asp), indicating that the carbohydrate group attached to Asn-131 may affect host range (Gitelman *et al.*, 1986; Gambaryan *et al.*, 1998).

Competitive inhibitors, such as soluble receptor analogs that are present in the serum of many species, may also play a role in influenza virus host range restriction (Ryan-Poirier and Kawaoka, 1991). For example, α_2-macroglobulins present in horse and guinea pig serum were shown to strongly inhibit hemagglutination as well as infection of MDCK cells by human H3 viruses with SAα2,6Gal receptor specificity, but did not affect equine and avian H3 virus infection (Rogers *et al.*, 1983). Similarly, recent studies indicate that SA residues on porcine surfactant protein D (pSP-D) may also influence host range, possibly by acting as natural inhibitors of influenza virus binding to cell-surface SA receptors (Hartshorn *et al.*, 2000; van Eijk *et al.*, 2002; Hawgood *et al.*, 2004). While it remains unclear if and to what extent pSP-D contributes to host range, it has been speculated that pSP-D interference may play a particularly important role in human-to-swine transmission of influenza viruses (van Eijk *et al.*, 2002).

NA

Like HA, the NA also contributes to influenza virus species specificity. Since efficient growth of influenza virus is dependent on balanced action between HA receptor-binding affinity and NA receptor-destroying activity (Baum and Paulson, 1991; Rudneva *et al.*, 1993; Gubareva *et al.*, 1996, 2002; McKimm-Breschkin *et al.*, 1996; Kaverin *et al.*, 1998, 2000; Baigent *et al.*, 1999; Kaverin and Klenk, 1999; Hughes *et al.*, 2000, 2001; Mitnaul *et al.*, 2000; Wagner *et al.*, 2000; Hatta *et al.*, 2001; Abed *et al.*, 2002), alterations in HA receptor-binding preference is often associated with changes in the NA's SA substrate specificity (i.e. cleavage activity of SAα2,3Gal versus SAα2,6Gal) and cleavage activity (Baum and Paulson, 1991; Kaverin *et al.*, 1998, 2000; Mitnaul *et al.*, 2000; Wagner *et al.*, 2000). This conclusion is supported by the finding that after introduction of the 1957 pandemic strain into the human population, the SAα2,6Gal cleavage activity of the avian NA increased (Baum and Paulson, 1991; Kobasa *et al.*, 1999), which suggests that the NA had adapted to the SAα2,6Gal preference of the virus's

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HA (Neumann and Kawaoka, 2006). Interestingly, at this point the virus also appeared to lose its ability to efficiently grow in ducks (Kobasa *et al.*, 2001).

The NA molecule is comprised of the enzymatically active head domain and a stalk region that is inserted into the viral envelope (Lamb and Krug, 2006). The length and amino acid sequence of the stalk region vary considerably among different viruses (Blok and Air, 1982) and stalk length has been shown to affect growth characteristics of viruses in embryonated chicken eggs (Castrucci and Kawaoka, 1993), cell culture (Luo *et al.*, 1993), and mice (Castrucci and Kawaoka, 1993). Viruses with long stalks grew to higher titers in embryonated chicken eggs than those with shorter NA stalks (Castrucci and Kawaoka, 1993). Mechanistically, this may be explained by the finding that viruses with a shortened NA stalk typically are released less efficiently from the cell since the enzymatic site in the head domain cannot effectively reach its substrate (Castrucci and Kawaoka, 1993; Luo *et al.*, 1993; Baigent *et al.*, 1999; Giannecchini *et al.*, 2006). Furthermore, a deletion in the NA stalk is commonly associated with adaptation of duck viruses to land-based poultry such as turkeys and chickens (Castrucci and Kawaoka, 1993; Matrosovich *et al.*, 1999; Wagner *et al.*, 2000; Gambaryan *et al.*, 2002) and is thought to occur in order to counterbalance changes in the receptor-binding properties of the HA (Baigent and McCauley, 2001). Nevertheless, viruses with short stalks can maintain their virulence in humans and poultry. For example, the HPAI H5N1 viruses isolated from land-based poultry in Asia contained a shortened stalk (Li *et al.*, 2004). Similarly, H5N1 viruses isolated from human patients in Hong Kong in 1997 possessed short NA stalks (Matrosovich *et al.*, 1999).

Polymerase complex

The largest body of evidence regarding the effects of the proteins in the polymerase complex on species specificity has implicated the PB2 gene. For example, Clements and coworkers (Clements *et al.*, 1992) reported that a human–avian reassortant virus that contained only the avian PB2 gene replicated efficiently in avian cells, but inefficiently in mammalian cells and in the respiratory tract of squirrel monkeys and human volunteers. Subsequently, research revealed that the switch in host range hinged on a single amino acid residue at position 627 (Glu in avian isolates; Lys in human isolates) (Subbarao *et al.*, 1993). Penn and coworkers identified additional amino acid residues in PB2 as potential contributors to host range (Penn, 1989). The influenza polymerase complex constitutes a multifunctional enzyme and the outcome of its interaction with the viral RNA is modulated by whether the 3′ and 5′ termini of the viral template are in a base-paired or single-stranded conformation (Lee *et al.*, 2003). Thus, it has long been hypothesized that temperature at the site of replication could impact the function of the polymerase complex and thereby determine the host tropism of influenza virus (McCauley and Penn, 1990; Baigent and McCauley, 2003). This scenario is particularly appealing in light of the finding that viral polymerase complexes derived from avian viruses, but not human viruses, exhibited cold sensitivity in mammalian cells, a characteristic that was mostly controlled by residue 627 of PB2 (Massin *et al.*, 2001). The importance of residue 627 in the control of influenza host range is further highlighted by the findings that an H7N7 HPAI isolated from a patient in The Netherlands contained a Lys substitution at position 627 (Fouchier *et al.*, 2004) and several of the H5N1 strains isolated from humans in Asia were also characterized by Lys at residue 627 (Puthavathana *et al.*, 2005). In addition, a recent study by Mase and colleagues revealed that viruses isolated from mice infected with H5N1 (without prior adaptation to mice) all acquired the Glu-to-Lys substitutions at position 627 of the PB2 (Mase *et al.*, 2006). Finally, H5N1 isolates recovered from six tigers in 2004 also contained Lys at residue 627 (Amonsin *et al.*, 2006). Taken together, these observations suggest that the mutation at residue 627 may be a key determinant of influenza host range. Interestingly, studies by Hatta and coworkers indicated that the same Gly-to-Lys substitution at position 627 in the PB2 protein also influenced pathogenicity as well as cell tropism of a highly pathogenic H5N1 virus isolated in Hong Kong in 1997 (Hatta *et al.*, 2001).

Effects on host range have also been identified for the remaining two members of the polymerase complex: PA and PB1. For instance, the introduction of an avian PB1 into a human virus resulted in a decrease in replication efficiency in MDCK cells, as well as in squirrel monkeys, but did not affect virus replication in chicken kidney cells (Snyder *et al.*, 1987).

Apart from temperature sensitivity, amino acid substitutions in the polymerase proteins may influence host range by altering interactions of the polymerase complex with host cell factors. Host factors that were found to modulate viral RNA synthesis *in vitro* include RNA polymerase activating factors (RAF1 and 2), polymerase release factor (PRF), and RNA polymerase inhibiting factor 1 (RIF1) (Honda and Ishihama, 1997).

NP, M, and NS proteins

During virus replication, the influenza NP is modified by host-cell-derived phosphokinases (Lamb and Krug, 2006). As the phosphorylation pattern of the NP protein appears to determine the extent to which a particular cell line supports virus growth (Kistner *et al.*, 1985), it has been hypothesized that NP is a significant determinant of species specificity (Scholtissek *et al.*, 1985; Tian *et al.*, 1985; Snyder *et al.*, 1987; Abe *et al.*, 2004). Experiments

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using temperature-sensitive mutants of a HPAI H7N1 virus (A/FPV/Rostock/1/34) demonstrated that, with the exception of NP and HA, all remaining gene segments of the fowl plague virus could be replaced by corresponding genes of any strain, irrespective of the lineage of the rescuing virus (Scholtissek *et al.*, 1978, 1985). Furthermore, sequence analyses suggest that the NP gene has evolved into five distinct, host-specific lineages: two equine lineages, one pig and human lineage, one aquatic bird lineage, and one lineage in other avian species (Webster, 1997).

The influenza M1 protein plays an essential role in viral assembly and has a variety of functions, including association with influenza virus RNP complexes. The M2 is an integral membrane protein and functions as an ion channel (Pinto *et al.*, 1992; Holsinger *et al.*, 1994; Lamb and Krug, 2006). Employing human–avian reassortant viruses containing the avian M and NP genes, both gene segments were found to be associated with reduced replication of the reassortants in the respiratory tract of squirrel monkeys (Tian *et al.*, 1985). Further evidence for the M gene's contribution to influenza host range stems from co-infection experiments selecting for reassortant viruses with the human virus M gene and the HA gene derived from the avian virus. While the M segment of an earlier human virus was found to support efficient growth of the reassortants, M genes derived from more recent human strains did not cooperate with the avian HA (Scholtissek *et al.*, 2002).

Like the polymerase complex, the internal proteins may exert their effects on host range through interactions with cytoplasmic and nuclear host cell components (Brown, 2000a). For example, during infection, the influenza NP binds to actin, as well as karyopherins 1 and 2. Similarly, NS1 interacts with a number of cellular factors involved in mRNA processing [i.e. Cpsf, poly(A)-binding protein II and PKR] (Lamb and Krug, 2006), as well as other host factors with undefined function (NS1-BP and NS1-1) (Wolff *et al.*, 1996, 1998). Thus, it is conceivable that the quality of these protein-to-protein interactions may have an impact on influenza species specificity. However, to what extent such protein–protein interactions determine host range has yet to be determined.

Concluding remarks

In the past decade, a number of viruses have emerged from animal populations. These include HIV (Levy *et al.*, 1984; Wain-Hobson *et al.*, 1991), hendravirus (Murray *et al.*, 1995), and the coronavirus causing severe acute pulmonary syndrome (SARS) (Kuiken *et al.*, 2003). In addition to these newly recognized viruses, re-emerging viruses are burdening the human population at a seemingly increasing frequency (Morse, 1997). One of our most familiar viruses, influenza A virus, also falls into this category. The recent resurgence of H5N1 influenza A viruses in poultry, wild waterfowl, cats and people throughout large parts of Asia, the Middle East, Europe, and Africa further highlights the possibility that viruses originating in an animal species could spark a new influenza pandemic (de Jong *et al.*, 1997; Cox and Subbarao, 2000; Laver *et al.*, 2000; Horimoto and Kawaoka, 2001; Hatta and Kawaoka, 2002; Katz, 2003; Belshe, 2005; Webster *et al.*, 2005; Ferguson, 2006; Kenny, 2006; Maldin and Criss, 2006). An important reason why these viruses have not yet caused a full-blown pandemic is their apparent inability to spread efficiently from person to person (Hatta and Kawaoka, 2002; Katz, 2003; Capua and Alexander, 2004; Webster *et al.*, 2005; Kandun *et al.*, 2006; Shinya *et al.*, 2006). While there has been an explosion of data on the molecular determinants of influenza virus adaptation to a new host species within the last decade, much remains to be learned. In light of the importance of animal reservoirs in the ecology of influenza as well as the potential roles of pigs and terrestrial poultry as adaptation or 'mixing vessel' hosts, virus surveillance at the human–animal interface and genetic analysis of animal influenza viruses must remain a priority. The data collected will continue to provide important insights regarding the genetic basis of host adaptation and advance our understanding of the extent and impact of animal reservoirs of influenza A viruses.

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