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Natural history of highly pathogenic avian influenza H5N1

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ABSTRACT

The ecology of highly pathogenic avian influenza (HPAI) H5N1 has significantly changed from sporadic outbreaks in terrestrial poultry to persistent circulation in terrestrial and aquatic poultry and potentially in wild waterfowl. A novel genotype of HPAI H5N1 arose in 1996 in Southern China and through ongoing mutation, reassortment, and natural selection, has diverged into distinct lineages and expanded into multiple reservoir hosts. The evolution of Goose/Guangdong-lineage highly pathogenic H5N1 viruses is ongoing: while stable interactions exist with some reservoir hosts, these viruses are continuing to evolve and adapt to others, and pose an un-calculable risk to sporadic hosts, including humans.

Contents

1. Introduction

It has been speculated that influenza viruses have infected humans and animals since ancient times (Morens and Taubenberger, 2010). Influenza A, B, and C viruses are thought to have diverged from a common ancestor at an indeterminate time, and have formed multiple lineages, particularly influenza A viruses (Buonagurio et al., 1985; Palese and Shaw, 2007; Xu et al., 2011; Tong et al., 2012). Influenza A viruses exist in many different environments and utilize a variety of different host species (Webster et al., 1992; Reperant et al., 2009; Taubenberger and Kash, 2010; Tong et al., 2012) (Fig. 1). The ecology of these viruses is highly variable with respect to their interactions with each other (reassortment, competition), with their hosts (immunity, receptor availability, host temperature), and with their environment (ambient temperature, humidity, composition of sediment, salinity of water, pH) (Watanabe et al., 2012b; Webster et al., 1992).

Here we focus on the ecology of highly pathogenic avian influenza (HPAI) Goose/Guangdong (Gs/Gd)-lineage H5N1 by examining (1) the general characteristics of avian influenza viruses; (2) the adaptation of Gs/Gd-lineage H5N1 to domestic geese as

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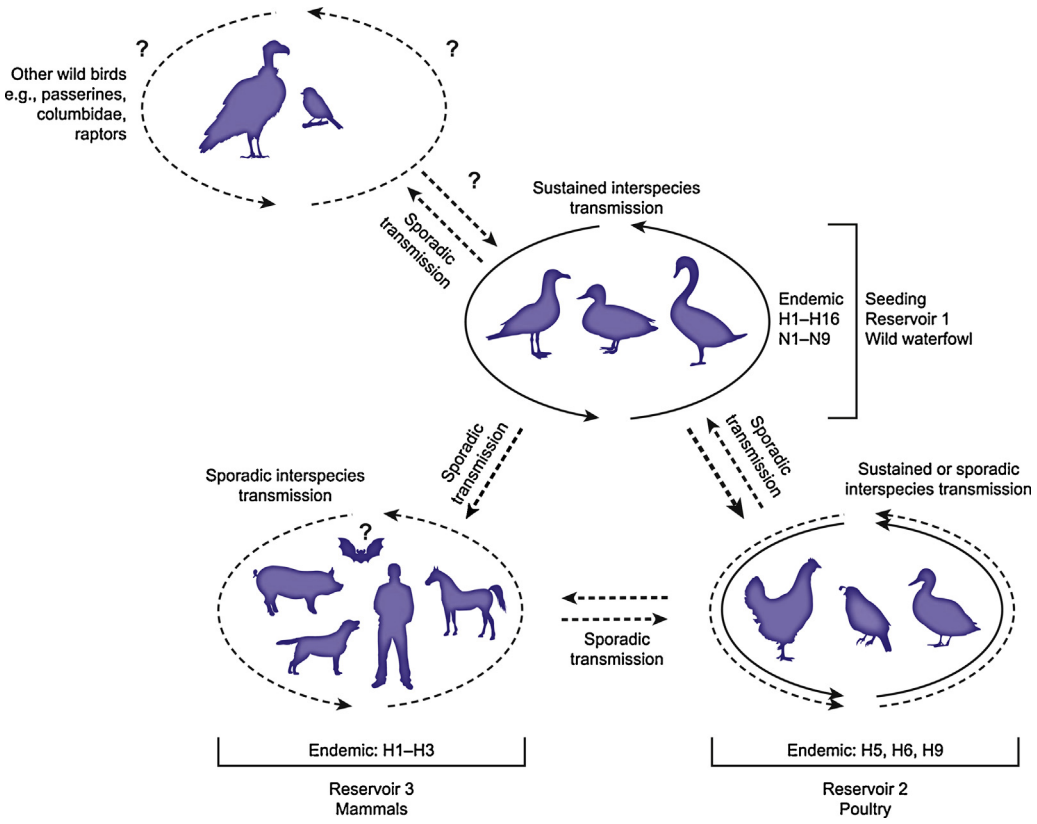

Fig. 1. Wild waterfowl represent the seeding reservoir of influenza A viruses. Three reservoir groups of influenza A viruses are shown: wild waterfowl, poultry, and mammals. Arrows indicate transmission of influenza A viruses between different host reservoir groups and circulation among species within each group. Dotted lines represent sporadic transmission, solid lines represent sustained transmission between different species. Question marks indicate unknown or unresolved transmission patterns. The hemagglutinin subtypes endemic in one or more species in each group are indicated. For wild waterfowl, endemic neuraminidase types are also indicated.

reservoir host; (3) unstable transition periods associated with changes in host range, virus genotype, and geographical range; and (4) ongoing adaptation of Gs/Gd-lineage H5N1 to wild waterfowl as host reservoir.

2. General characteristics of influenza A viruses

Influenza viruses of the *Orthomyxoviridae* family contain a negative-sense single stranded and segmented RNA genome and are differentiated into influenza A, B, and C. Influenza B viruses have historically caused yearly epidemic outbreaks in humans, while influenza C viruses have been largely associated with young children and pigs. Influenza A viruses are associated with yearly epidemics as well as sporadic pandemics and have a large animal reservoir amongst the wild aquatic birds of the world (Kimura et al., 1997; Webster et al., 2002; Palese and Shaw, 2007; Wright et al., 2007).

Influenza A viruses contain eight gene segments and encode at least 10 proteins: polymerase basic 1 (PB1), PB2, polymerase acid (PA), hemagglutinin (HA), nucleoprotein (NP), neuraminidase (NA), matrix 1 (M1), M2, nonstructural 1 (NS1) and 2 (NS2, also nuclear export protein – NEP) (as reviewed in Webster et al., 1992; and in Palese and Shaw, 2007). Additional to the 10 core proteins, several other viral proteins have been recently described with strain-specific or as yet unknown functions: PB1-F2 (Zamarin et al., 2006; McAuley et al., 2007; Chen et al., 2001, 2010; Krumbholz et al., 2011), PB1-N40 (Wise et al., 2009), PA-X (Jagger et al., 2012), and PA-N155 and PA-N182 (Muramoto et al., 2013).

HA, responsible for virus attachment to the host cell, is the major target of the humoral immune response. HA-specific immune pressure of a host population against influenza A is associated with ongoing antigenic changes and immune escape of virus subtypes (Smith et al., 2004; Wright et al., 2007).

The primary natural host reservoir of avian influenza A viruses (AIV) are wild waterfowl, particularly anatidae (i.e. ducks, geese, swans) in the order *Anseriformes* and scolopacidae (shorebirds/waders) and laridae (gulls, terns) in the order *Charadriiformes* (Stallknecht and Shane, 1988; Webster et al., 1992; Krauss et al., 2004, 2010; Olsen et al., 2006; Stallknecht and Brown, 2008) (Fig. 1). Sixteen HA types and nine NA types have been detected in viruses isolated from wild waterfowl. AIV are considered the ancestors of influenza A viruses of mammals (Scholtissek et al., 1978; Webster et al., 1992; Krauss et al., 2004, 2007, 2010; Fouchier et al., 2005; Wright et al., 2007; Garten et al., 2009; Guan et al., 2010; Hoye et al., 2010; Taubenberger and Kash, 2010; Vandegrift et al., 2010; Smith et al., 2009a,c).

The vast majority of AIV cause little to no disease in birds and are characterized by a HA cleavage site which relies on proteases of intestinal and respiratory tract mucosa (Bertram et al., 2010; Klenk et al., 1975; Lazarowitz et al., 1973). Low pathogenic avian influenza (LPAI) viruses replicate primarily in the intestinal tract of birds and it is generally agreed that wild waterfowl contract LPAI viruses mainly via fecal-oral inoculation (Krauss et al., 2004, 2010; Fouchier et al., 2005; Hoye et al., 2010; Vandegrift et al., 2010). Duration and magnitude of virus shedding is highly species- and virus strain-specific and also includes the avian respiratory tract (Webster et al., 1978, 1992; Stallknecht and Brown, 2008; Costa et al., 2011; Hinshaw et al., 1980a,b). Virus shedding from