

Host-range barrier of influenza A viruses

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Abstract

Ample evidence suggests that all influenza viruses in mammals were probably derived from those in wild waterfowl at some time. In addition to those already established in mammals, the viruses have been transmitted to both mammals and to poultry from wild waterfowl and caused outbreaks in recent years. Experimentally, however, the viruses from one species of animals do not grow efficiently in other species. For example, human influenza viruses do not replicate in ducks or in horses, indicating their host range restriction. This paper reviews current knowledge on the host-range restriction of influenza viruses, focusing on the role of the hemagglutinin (HA). © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Influenza A viruses have been isolated from a variety of animals, including pigs, horses, minks, seals, whales and birds, as well as humans (Webster et al., 1992). Interspecies transmission of influenza viruses, although rare, has been detected. For example, avian H1N1 (Scholtissek et al., 1983) and human H3N2 (Tumova et al., 1980; Ottis et al., 1982; Mancini et al., 1985; Haesebrouck and Pensaert, 1988; Wibberley et al., 1988) viruses have been transmitted to pigs, swine H1N1 viruses to humans (Rota et al., 1989), and avian viruses to horses (Guo et al., 1992), seals (Webster et al., 1981; Hinshaw et al., 1984), whales (Hinshaw et al., 1986), and mink (Klingeborn et al., 1985).

Experimentally, avian influenza viruses do not replicate efficiently in humans (Beare and Webster, 1991) and other primates (more than a 100-fold decrease) (Murphy et al.,

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1982). Although immunity to currently circulating human H1 and H3 viruses may explain the poor replication of these subtypes of avian viruses in human hosts, it does not account for the limited replication of avian viruses of other subtypes not found in humans (i.e. H4, H6, H9 and H10) (Beare and Webster, 1991). Similarly, human viruses do not replicate efficiently in waterfowl when introduced by natural routes (Hinshaw et al., 1983). However, avian influenza viruses can be directly transmitted to humans, as indicated by the recent incident in Hong Kong (Claas et al., 1998; Subbarao et al., 1998), but the probability that they will establish themselves in human populations is low, thereby limiting opportunities for the generation of human-avian reassortant viruses. How, then, does one explain the apparent breach of this host-range restriction during the generation of pandemic influenza viruses? Scholtissek et al. (1985) proposed that pigs may serve as 'mixing vessels' for the production of reassortant influenza viruses. Indeed, a variety of avian and human influenza viruses replicate efficiently in pigs upon experimental infection (Hinshaw et al., 1981; Kida et al., 1994). Phylogenetic and epidemiologic analyses indicate that avian and human viruses have been transmitted to pigs in nature (Gorman et al., 1991; Schultz et al., 1991), and that they have reassorted in pigs (Castrucci et al., 1993) and been transmitted to humans (Claas et al., 1994). Despite this considerable body of circumstantial evidence, the molecular basis for human-avian viral gene reassortment in pigs remained unknown.

Although influenza A viruses uniformly recognize cell surface oligosaccharides with a terminal sialic acid, their receptor specificities vary. Most avian and equine influenza viruses preferentially bind to the *N*-acetylneuraminic acid- α 2,3-galactose (NeuAc α 2,3-Gal) linkage on sialyloligosaccharides, while human influenza viruses prefer the NeuAc α 2,6Gal linkage (Rogers and Paulson, 1983). However, little was known about the sialyloligosaccharide structures at viral replication sites in pigs or in other common hosts. Since the presence or absence of viral species-specific receptors on host cells would have a key role in replication of influenza A viruses in each host, we sought to identify the types of sialyloligosaccharides at the replication sites of various influenza viruses, and to test their suitability for binding viruses.

2. Molecular basis for the generation of influenza A viruses in pigs with pandemic potential

Since avian and human influenza viruses show different receptor preferences, NeuAc α 2,3Gal versus NeuAc α 2,6Gal (Rogers and Paulson, 1983), and epithelial cells lining human trachea possess mainly the latter sialyloligosaccharide (Couceiro et al., 1993), we considered that one of the determinants of the replicative potential of such viruses in different hosts might be the sialic acid-galactose linkage present on sialyloligosaccharides. A binding assay using two sialyloligosaccharide (NeuAc α 2,3Gal and NeuAc α 2,6Gal)-specific lectins showed that the epithelial cells of duck intestine mainly contains NeuAc α 2,3Gal, but not NeuAc α 2,6Gal, whereas pig trachea contains both linkages. These results, together with the finding of Couceiro et al. (1993), suggest that the lack of a suitable receptor accounts for the inefficient replication of human viruses in duck intestine and of avian viruses in humans. Moreover, detection of both

linkages in pig trachea provides a molecular basis for efficient replication of human and avian influenza viruses in this host (Hinshaw et al., 1981; Kida et al., 1994), and, hence, genetic reassortment of these viruses.

With continued replication in pigs, we also found that the avian viruses appear to undergo a shift in their receptor specificity to NeuAc α 2,6Gal linkages exclusively. These observations suggest at least two mechanisms, both dependent on HA-receptor interactions, that would permit pigs to serve as intermediate hosts for the generation of pandemic influenza viruses. In one, avian and human viruses would reassort in the classical fashion, giving rise to a hybrid strain with pandemic potential. In the other, an avian virus would acquire the ability to bind efficiently to human cell-surface receptors so that it could be readily transmitted to a human host without the requirement for genetic recombination. These models may not be mutually exclusive. Quite possibly, an avian virus could combine with a human virus before or after becoming adapted to the NeuAc α 2,6Gal linkage, resulting in a reassortant with enhanced proliferative capacity.

Although circumstantial evidence (Scholtissek et al., 1985; Castrucci et al., 1993; Claas et al., 1994) favors involvement of pigs in genetic reassortment, direct transmission of an avian virus to human does occur as exemplified by the recent incident in Hong Kong (Claas et al., 1998; Subbarao et al., 1998) and the possibility of reassortment in humans or adaptation to recognize receptors in humans cannot be discounted. With the rarity of human influenza pandemics, it is difficult to predict which of these models is more likely to generate a potentially hazardous virus.

3. Receptor specificity of influenza A viruses from sea mammals correlates with sialyloligosaccharides present in the lungs of these animals

For the purpose of further assessing the correlation between host receptors and the receptor specificity of influenza A viruses, we examined the receptors for influenza A virus in seal and whale lungs. Lectin assays showed that SA α 2,3Gal, but not SA α 2,6Gal, was found in both seal and whale lungs.

Correspondingly, seal and whale influenza viruses preferentially recognized SA α 2,3-Gal, rather than SA α 2,6Gal. These data indicate that the presence of receptor molecules at the replication site of influenza virus corresponds to the receptor specificity of the viruses from sea mammals. They also provide the molecular support for the transmission of avian influenza virus directly to sea mammals (Webster et al., 1981; Hinshaw et al., 1984, 1986).

4. Conclusion and future directions

Although, in this study, we focused on the receptor specificity of the HA, the genes of influenza A viruses encoding internal proteins as well as the NA may also play roles in host-range restriction. For example, the NP and M genes are responsible for the attenuation of avian viruses in squirrel monkeys (Tian et al., 1985). Depending on the human influenza viruses used to prepare reassortants with avian viruses, a combination of

polymerase genes could also affect replication in squirrel monkeys (Snyder et al., 1987). Further studies are needed to fully understand the contribution of these gene products to host-range restriction.

Many new viral pathogens have emerged in man (e.g. human immunodeficiency virus, influenza A viruses, Ebola virus, Hantan virus, monkeypox virus and Born disease virus). Learning the precise molecular changes that allow these agents to cross host-species barriers is essential in developing effective means of prevention. The evidence we present supports the role of pigs as a source of potentially hazardous influenza A viruses, arising through classical genetic reassortment or a novel adaptation to human virus receptors, or perhaps through both these mechanisms. Thus, continued intensive monitoring of swine populations for avian-like influenza viruses should be an integral part of global health planning.

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