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Roll of hemagglutinin gene in the biology of avian influenza virus

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ABSTRACT

The hemagglutinin (HA), the major envelope glycoprotein of influenza, plays an important role during the early stage of infection, and changes in the HA gene prior to the emergence of pathogenic avian influenza viruses. The HA protein controls viral entry through membrane fusion of the viral envelope with the host cell membrane and allows the genetic information released to initiate new virus synthesis. Sharp antigenic variation of HA remains the critical challenge to the development of effective vaccines. Therefore, we highlight the role of HA in need of review: structure of HA, the fusion process and the HA receptor binding specificity in interspecies transmission and the impact of multiple mutations at antigenic sites and host antibodies to the parental virus, and the host susceptibility to productive infection by the drift strains.

1. Introduction

The genome of influenza viruses is composed of eight segments, which encode at least 10 different viral proteins. The structural proteins are hemagglutinin (HA), neuraminidase, and membrane ion channel. The internal proteins are matrix protein and nucleoprotein. The RNA polymerization complex consists of polymerase basic protein (PB) 1, PB 2 and polymerase acidic protein[1]. The non-structural (NS) proteins (NS1) and (NS2), are collectively known as nuclear export protein (Figure 1). HA is the most important protein of influenza virus that it encoded by gene segment 4 of influenza virus gene[2].

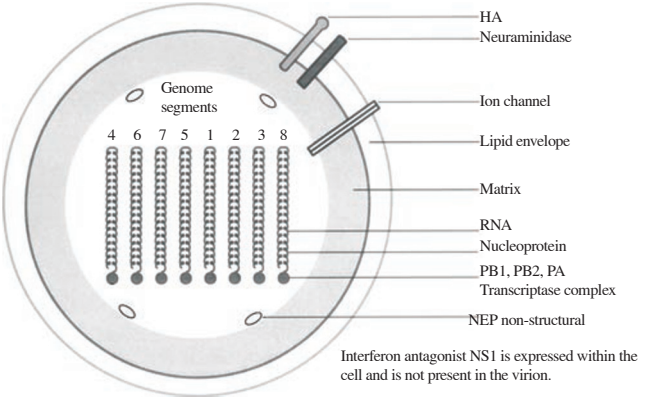

Figure 1. Structural proteins in the mature virion.
PA: Polymerase acidic protein; NEP: Nuclear export protein.

To date, 16 HA (1–16) subtypes have been detected in aquatic birds and poultry[3]. The first critical step in viral infection is

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attachment of the virus HA protein to the host cell receptor, including sialic acid[2]. The HA gene is the initial determinant of high pathogenicity in hosts. The cleavage of the HA into the HA1 and HA2 proteins is critical for the virus to be infectious and produce multiple cycles of replication[4].

The HA receptor binding specificity is changed early after interspecies transmission of an aquatic birds virus to humans and pigs and, therefore, may be a requisite for the highly effective replication and spread which are characterized by epidemic strains[5].

2. Structure

The crystal structure of HA molecule is a trimer that consists of two structurally different regions: a stem, a triple-stranded coiled-coil of α-helices, and a globular head of antiparallel β-sheet, positioned atop the stem (Figure 2)[4]. The head is composed of the sialic acid receptor binding site that is surrounded by the predicted antigenic variation determinants and these sites are designated by A, B, C, and D in the H3 subtype, while for H1 subtype, sites are designated by Sa, Sb, Ca1, Ca2, and Cb[4].

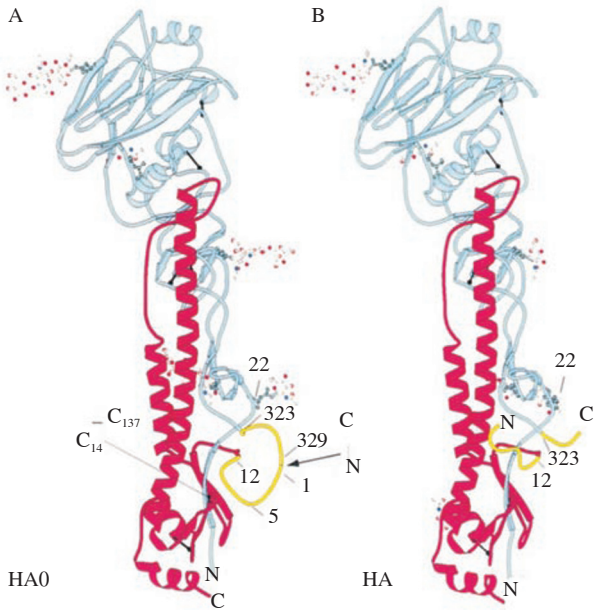

Figure 2. Structure of the precursor (R239Q HA0s) cleavage site before and after cleavage[6].

During virus replication, influenza virus HA, biosynthetic precursor HA0 is cleaved by serine proteases into HA1 and HA2 and this post-translational modification is essential for viral infectivity. The HA2 portion of HA molecule is assumed to mediate the viral envelope fusion with host cell membranes, while the HA1 portion contains the antigenic and receptor binding sites[7,8]. Antibodies against HA can neutralize the virus infectivity, so virus strains evolve frequent amino acid alterations at the antigenic sites; however, the stem-head region of the HA molecule remains conserved between subtypes and strains. The accumulation of minor changes is involved in a process called antigenic drift. Finally, multiple mutations at antigenic sites may lead to a virus strain that is no longer effectively neutralized by host antibodies to the parental virus, and the host can be also susceptible to productive infection by the drift strain[9-14].

3. Virus attachment

The HA proteins control fusion of the viral envelop with the host cell membrane and allow the genetic information released to initiate new virus synthesis. The highly conserved HA fusion peptide also mediates this process[15].

The fusion peptide exists on the HA2 region of the mature protein and exposes on further cleavage into HA1 and HA2 subunits (Figure 3). After the virus particles go in an endocytic vesicle by endocytosis and the pH is decreased, the HA2 undergoes a striking conformational change that brings the fusion peptide close to the vesicle membrane, allowing fusion and extrusion of the contents into the cellular cytoplasm. Therefore, cleavage of the HA polyprotein is critical for the exposure of the fusion peptide and the released fusion peptide is utterly crucial for the initiation of infection. Influenza viruses identify *N*-acetylneuraminic acid on the host cell surface. Sialic acids are nine-carbon acidic monosaccharide usually found at the terminal of many glycoconjugates. Thus, they are ubiquitous in many cell types and in many species of animal. The carbon-2 of the terminal sialic acid can attach to the carbon-3 or carbon-6 of galactose, forming α-2, 3- or α-2, 6-linkages; these distinct linkages lead to a unique steric configurations of the terminal sialic acid (Figure 4). The HA spikes on the surface of influenza viruses distinguished and bound to the sialic acid moiety, which have a preferentially specificity for α-2, 3- or α-2, 6-linkages. In human tracheal epithelial cells, α-2, 6-linkages are prevalent, while α-2, 3-linkages are most common in gut epithelium of duck. Sialic acids with terminal α-2, 3-linkages are also presented in human respiratory epithelium, however, they are less abundant than those with α-2, 6-linkages[16-18]. Consequently, avian influenza viruses can involve humans and other primates are less efficiently involved than human strains[19,20].

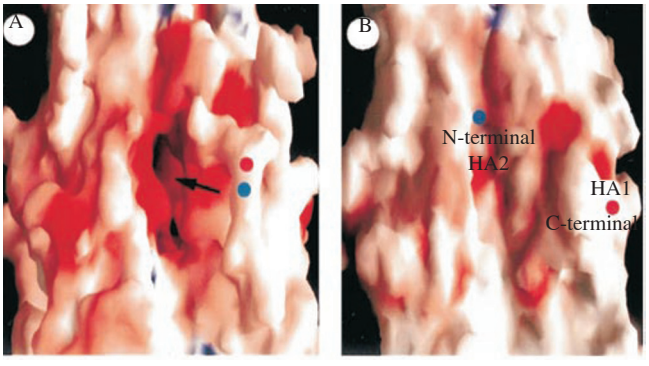

Figure 3. A surface cavity in HA0 adjacent to the cleavage site filled by the fusion peptide after cleavage[21].