Glycan Receptor for Influenza Virus

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Abstract: Influenza viruses are found in wide range of animals, including humans, in nature. When avian and human viruses simultaneously infect an intermediate host, such as pigs, genetic recombination can occur between these viruses. There is concern regarding interspecies transmission, both initial animal-to-animal infection and outbreaks of pandemic viruses in the human population.

Hemagglutinin (HA) is a trimeric protein expressed on the influenza virus membrane. The globular head domain of the HA contains a receptor-binding site (RBS) that mediates virus attachment to host cells. Sialic acid (SA)-containing glycans, termed sialoglycans expressed on the host cell surface, are considered to serve as influenza virus receptors in both interspecies transmission and epidemics in a specific host. Influenza virus HAs recognize specific linkages of sialic acids in the receptors. Recently, histochemical studies using lectins specific for sialic acid linkages demonstrated that the characteristic distribution of sialoglycans is associated with interspecies viral transmission.

To understand interspecies transmission of influenza viruses, it is essential to elucidate the molecular mechanisms of the interaction between influenza virus HAs and sialoglycan receptors expressed on different host cells. This review article focuses on the structure and distribution of receptors for human and other animal influenza viruses, and on molecular mechanisms underlying influenza virus recognition with specific glycan structures. This review also introduces synthetic glycopolymers carrying multivalent sialylated carbohydrates, which have been applied not only to address the molecular mechanisms of virus - host cell interaction, but also inhibition of influenza virus infection.

Keywords: Influenza virus, receptor, sialoglycan, sialic acid, glycopolymer.

INTRODUCTION

Glycan molecules, such as glycoproteins, glycosphingolipids, and proteoglycans, are present ubiquitously on the cell surface. They have diverse carbohydrate structures on their molecules [1]. Among them, glycoproteins and glycosphingolipids containing sialic acid (SA) and specific carbohydrate structures are strongly associated with influenza virus infection, particularly host and tissue tropism [2]. Glycoproteins consist of two functional parts: a polypeptide chain and a carbohydrate portion. They are further classified into two categories on the basis of linkage between polypeptide and carbohydrate portions. First, *N*-glycan represents carbohydrate chains attached to asparagine residues on a polypeptide [3, 4]. The anomeric carbon of *N*-acetylglucosamine (β-GlcNAc) residue at the reducing terminal of carbohydrate chain is connected to nitrogen of the amide of asparagine residue by an *N*-glycosidic bond. A typical mammalian *N*-glycan carrying a carbohydrate chain that can be recognized by influenza virus is shown in Fig. (**1**). A characteristic feature of the *N*-glycan structure is an elongated and branched carbohydrate chain linked with a mannose core, which consists of Galβ1-4GlcNAc unit repeats, termed lactosamine (LacNAc) repeats. Second, *O*-glycan generally represents a short carbohydrate sequence that consists of SAα2-3Galβ1-3GalNAc residues attached to a serine or threonine residue on a polypeptide. This glycan is typically found in mucin-type glycoproteins. A branching enzyme, termed core2 *N*-acetylglucosaminyltransferase (Core2 GlcNAc-T) contributes to elongation of the *O*-glycan chain (Fig. **1**) [5, 6]. The elongated *O*-glycan chain carries LacNAc repeats and nonreducing sialic acid residues similar to those on *N*-glycan. Glycosphingolipid is the other glycan that can also be recognized by influenza virus. This glycan molecule consists of a carbohydrate moiety and ceramide, a lipid portion. There are many molecular species in glycosphingolipids on the basis of diversity of the carbohydrate moiety. Some carry the same carbohydrate structures as *N*- and *O*-glycans on glycoproteins. A glycosphingolipid containing a LacNAc unit like *N*- and *O*-glycans is shown in Fig. (**1**).

Nonreducing termini of glycans on both glycoproteins and glycosphingolipids are predominantly modified with SAs. SA-containing glycans are involved in a number of biological and pathological events, such as differentiation, tumor metastasis, and inflammation [1, 2, 7-9]. Carbohydrate structures containing sialic acid residues play critical roles in cell - cell recognition and cell - pathogen interactions. SA is an essential determinant for influenza virus adsorption to the host cell surface. There are more than 20 molecular species

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Sialylated glycoprotein

N-glycosylation (triantennary type)

SAα2-3/6(Galβ1-4GlcNAcβ1-3)$_n$Galβ1-4GlcNAcβ1-6
Manα1-6
SAα2-3/6(Galβ1-4GlcNAcβ1-3)$_n$Galβ1-4GlcNAcβ1-2 Manβ1-(4GlcNAcβ1-)$_2$Asn
SAα2-3/6(Galβ1-4GlcNAcβ1-3)$_n$Galβ1-4GlcNAcβ1-2Manα1-3

O-glycosylation (Core 2 type)

SAα2-3/6(Galβ1-4GlcNAcβ1-3)$_n$Galβ1-4GlcNAcβ1-6
GalNAcα1-Ser/Thr
SAα2-3Galβ1-3

Sialylated glycosphingolipid

IV$^{2/6}$SAnLc$_4$Cer (Sialylparagloboside)

SAα2-3/6Galβ1-4GlcNAcβ1-3Galβ1-4Glcβ1-1'Cer

Fig. (1). Representative sialoglycans expressed on the plasma membrane.SA, sialic acid (Neu5Ac or Neu5Gc); Gal, galactose; GlcNAc, *N*-acetylglucosamine; GalNAc, *N*-acetylgalactosamine; Man, mannose; Glc, glucose; Cer, ceramide. SAα2-3/2-6 indicates sialic acid (Neu5Ac or Neu5Gc) with α2-3 or α2-6 linkage.

of SA in nature [10]. Neu5Ac and Neu5Gc as shown in Fig. (**2**) are two major SAs present in mammalian cells. Neu5Gc is biosynthesized from Neu5Ac by hydroxylation. Hydroxylated SA is characteristically distributed in certain animals, such as the horse, pig, and mouse, but not in humans. On the other hand, Neu5Ac is ubiquitously present in all animals. Both sialic acids can be recognized by influenza virus. Linkage of SA to the inner galactose residue also shows several variations. Among them, SAα2-3 and SAα2-6 residues can be critically involved in host recognition by influenza viruses derived from different animals.

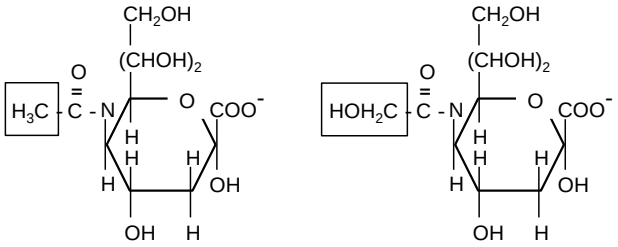


Fig. (2). Chemical structures of sialic acid.The squares emphasize structural differences between Neu5Ac and Neu5Gc.

In this review article, the structure and the distribution of sialoglycan receptors for human and other animal influenza viruses are summarized. The molecular mechanisms underlying influenza virus recognition with specific glycan structures are also described and discussed. Finally, this review focuses on possible application of synthetic glycopolymers carrying multivalent sialylated carbohydrates for not only addressing the molecular mechanisms of virus - host cell interaction, but also inhibition of influenza virus infection.

STRUCTURE OF INFLUENZA VIRUS RECEPTOR

Influenza virus agglutinates red blood cells by adsorption of a viral protein termed hemagglutinin (HA) with sialoglycan receptors. Sialic acid residues are essential for virus-induced agglutination of red blood cells. The structures of sialoglycan receptors effectively involved in virus adsorption to the host cell surface have been studied over the past 3 decades. A thorough and systematic investigation of virus binding to sialoglycans demonstrated the functional carbohydrate structures for virus-specific host interaction. Table **1** summarizes the dominant carbohydrate determinants involved in host recognition of influenza viruses isolated from various species. The sialoglycan receptors in all host species have SA-linked LacNAc residues as nonreducing terminal carbohydrate chains. The functional importance of SA linkage attached to LacNAc residue for virus-specific host interaction has been elucidated. SA-containing carbohydrate molecules expressed on the host cell surface are critical determinants of both interspecies transmission and epidemics in a specific host. Two SA linkages, SAα2-3 and SAα2-6, are significantly associated with effective transmission of influenza virus. SAα2-6 linkage is predominantly recognized by human and swine influenza viruses, but not avian or equine viruses. In contrast, avian and equine viruses bind exclusively to SAα2-3-linked galactose residues. Avian viruses can recognize two types of core carbohydrate with SAα2-3 linkage, authentic SAα2-3LacNAc and mucin-type SAα2-3Galβ1-3GalNAc that is typically found in *O*-linked glycoproteins. Viruses isolated from swine, which is considered an intermediate host between avian and human, equally recognize both SAα2-3-linked and SAα2-6-linked LacNAc determinants. Recent progress in defining the receptor glycan structure highlights the significance of an elongated core carbohydrate chain comprised of at least three repeated LacNAc units for human and swine virus recognition [21, 22, 30, 33-35]. Elongation of the core carbohydrate chain contributes significantly to enhancement of binding affinity of these viruses. In contrast, influenza viruses from other animals, such as avian and equine viruses, prefer a single LacNAc unit with SA to the elongated LacNAc. Modification of SA and/or core carbohydrate chains, such as hydroxylation and sulfation, may act as critical determinants of virus recognition [18, 22, 25, 36, 54]. The molecular species of SA are considered to be related with certain virus recognition. Equine virus favors Neu5Gc, a hydroxylated SA, as com-

Table 1. Receptor Carbohydrate Structures Recognized in Various Host Species

Carbohydrate Determinant	Repeating Unit	Host
Neu5Acα2-3(LacNAc)$_n$	n=1	avian, swine
Neu5Acα2-6(LacNAc)$_n$	n=3	human, swine
Neu5Gcα2-3(LacNAc)$_n$	n=1	equine, canine, avian

Neu5Ac and Neu5Gc, *N*-acetyl and *N*-glycolyl neuraminic acid.LacNAc, Galβ1-4GlcNAcβ1- residue.

pared to other animal virus recognition [18]. Neu5Gc may be involved in interspecies transmission between horse and other animals as well as epidemics in horses. Several lines of evidence indicated that not only highly pathogenic avian viruses, such as H5N1, but also the 1918 Spain flu virus (H1N1) strain bound effectively to sulfated sialoglycans with highly negative charges [22, 25].

MOLECULAR BASIS OF INTERACTION BETWEEN INFLUENZA VIRUSES AND HOST RECEPTORS

Hemagglutinin expressed as a homotrimer on the viral membrane is responsible for host - virus interaction. This protein is cleaved by the action of host proteases, resulting in generation of two functional domains, *i.e.*, HA1 and HA2. Several HA subtype proteins have been structurally resolved by X-ray crystallography [37-46]. The HA protein structure enables us to understand the molecular basis of the functional interaction between virus particles and host glycan receptors. In common with all subtypes of HA protein, the receptor binding site (RBS) is located on the globular head of HA1. Table **2** summarizes the amino acid residues on HA1 significantly related to receptor sialoglycan recognition. Most of the amino acid replacements are found in RBS. In human and avian H1 viruses, two amino acid residues at positions 190 and 225 in RBS contribute strongly to recognition to sialoglycan receptors containing Neu5Acα2-3Gal residues [20-22]. Aspartic acid residues at both 190 and 225 are typically found in human seasonal H1 viruses, which exclusively recognize Neu5Acα2-6LacNAc as the receptor. In contrast, avian viruses that have Glu and Gly residues at positions 190 and 225, respectively, bind Neu5Acα2-3sialoglycans with either LacNAc or Galβ1-4GalNAc core carbohydrate as receptors. Recent studies indicated distinct receptor recognition by human pandemic H1N1 viruses. The 1918 Spain flu virus, which possessed Asp at both 190 and 225, showed very similar receptor binding to human seasonal H1N1 [19, 24-27]. Some Spain flu strains with replacement to either Glu at 190 or Gly at 225 can bind equally to both Neu5Acα2-3 and Neu5Acα2-6Gal residues [27]. However, the 2009 pandemic H1N1 viruses identified to date recognize both Neu5Acα2-3 and Neu5Acα2-6Gal residues [33]. In human H2 and H3 seasonal viruses, three amino acid residues at positions 205, 226, and 228 are related to receptor sialoglycan recognition. Serine at 205 and 228 and Leu at 226 are essential for virus recognition of Neu5Acα2-6LacNAc as a receptor [11-17, 19]. On the other hand, avian H3 viruses with Gln at 226 and Gly at 228 bind exclusively to Neu5Acα2-3LacNAc. Studies on highly pathogenic avian influenza (HPAI) viruses, such as H5N1 and H7N7, highlight receptor sialoglycans strongly related to interspecies transmission between birds and humans [26, 28-30, 32]. Several amino acid residues have been shown to be involved in distinction of sialoglycan recognition. Both human and avian H5N1 HPAI strains show exclusive binding to Neu5Acα2-3LacNAc. In H5N1 HPAI strains isolated from humans, two major amino acid replacements caused alteration of receptor binding. A single or double replacement of Gln to Arg at 192 or Leu to Val at 129 and Ala to Val at 134, respectively, result in a change in unique recognition to Neu5Acα2-3LacNAc to dual recognition to Neu5Acα2-3 and Neu5Acα2-6 LacNAc [28, 29]. Similarly, replacement of Gln to Arg at 192 in avian H5N1 HPAI isolates causes binding to both Neu5Acα2-3 and Neu5Acα2-6 LacNAc [28].

DISTRIBUTION OF INFLUENZA VIRUS RECEPTORS

Human influenza viruses propagate in the epithelium of the respiratory organs, such as the nasopharynx, oropharynx, bronchioles, and lungs in humans. On the other hand, avian viruses proliferate predominantly in the epithelium of intestinal tissues, duodenum, cecum, and colon. It is reasonable to suggest that the expression of receptors specifically recognized by distinct influenza viruses should be consistent with the tissue tropism of each virus. Therefore, the distribution of virus receptors was investigated by histochemical analysis with two lectins, MAA and SNA, which react specifically with Neu5Acα2-3 and Neu5Acα2-6 residues, respectively. Table **3** presents a summary of the receptor distribution in major influenza virus hosts, such as human and birds. In the human respiratory tract, sialoglycans with Neu5Acα2-6 linkage, but not Neu5Acα2-3 linkage, are detected exclusively in tissues of the upper respiratory tract from the nasopharynx to the bronchi. Several lines of evidence also indicated that sialoglycans containing both Neu5Acα2-3 and Neu5Acα2-6 linkages are present in the human lower respiratory tract, such as bronchioles and lung alveoli [48-51]. In addition, the expression of SA linkages is related to cell types of the human airway epithelium. It is well known that there are morphologically distinct ciliated and nonciliated cells in the airway epithelium. These cell types each show a single type of SA linkage—Neu5Acα2-3 residues are detected specifically in ciliated cells, while Neu5Acα2-6 residue is exclusively in nonciliated cells [47]. Human and avian influenza viruses, including HPAI H5N1 viruses, have been examined for infection of the human respiratory tract. The results indicated that the tissue and cellular distributions of specific SA linkages are consistent with sialoglycan recognition of human and avian viruses in most cases [48, 50]. They also indicate a

Table 2. Sialoglycan Receptors Recognized by Influenza Virus Type A

Virus Subtype	Species	Sialoglycan Predominantly Recognized with Virus	HA Amino Acid Residue Related with Recognition	Ref
H1				
(seasonal)	*Human*	Neu5Acα2-6[$LacNAc_n$ ($n \geq 2$)]	190D/225D	[20-22]
	Avian	Neu5Acα2-3LacNAc or Neu5Acα2-3Galβ1-4GalNAc	190E/225G	[20-22]
	Swine	Neu5Acα2-3/2-6LacNAc		[22]
(1918 Spain flu)	*Human*	Neu5Acα2-6[$LacNAc_n$ ($n \geq 2$)]	190D/225D	[19, 24-27]
		Neu5Acα2-3/2-6LacNAc	190E or 225G	[19, 24-27]
(2009 pandemic)	*Human*	Neu5Acα2-3/2-6LacNAc		[33]
H2				
(seasonal)	*Human*	Neu5Acα2-3/2-6LacNAc	226L/228S	[11, 19]
H3				
(seasonal)	*Human*	Neu5Acα2-6[$LacNAc_n$ ($n \geq 2$)]	205S/226L/228S	[12-17, 34, 35]
		Neu5Ac/Neu5Gc	155Y/158G	[57]
	Avian	Neu5Acα2-3LacNAc	226Q/228G	[12-17, 34, 35]
	Equine	Neu5Ac/Neu5Gcα2-3LacNAc		[11, 18]
H5				
(H5N1 HPAI Clade I)	*Human*	Neu5Acα2-3LacNAc	182N/192Q, 129L/134A	[28-30]
		Neu5Acα2-3/2-6LacNAc	182N or 192R, 129V/134V	[28-30]
(H5N1 HPAI Clade II)	*Avian*	Neu5Acα2-3LacNAc	182N*/192Q	[28-30]
		Neu5Acα2-3/2-6LacNAc	192R	[28-30]
H7				
(H7N7 HPAI)	*Human*	Neu5Acα2-3LacNAc		[32]
(H7N2 LPAI)	*Human*	Neu5Acα2-3/2-6LacNAc		[32]
	Avian	Neu5Acα2-3/2-6LacNAc		[32]
H9				
(H9N2)	*Avian*	Neu5Acα2-3/2-6LacNAc	226Q	[23, 31]

LacNAc, Lactosamine residue (Galβ1-4GlcNAc). n, Number of lactosamine repeats.
*, Mutation of this amino acid results in abolition of virus binding. HPAI and LPAI,
High and low pathogenic avian influenza virus, respectively. α 2-3/2-6, Virus recognition of both α2-3 and α2-6 sialic acid linkages. Neu5Ac/Neu5Gc, Virus recognition of Neu5Ac and Neu5Gc.

possible mechanism by which avian viruses predominantly recognizing Neu5Acα2-3 residues can be transmitted from birds to humans, and that they can replicate in a restricted manner in the lower respiratory tract. This restriction may contribute to the inefficient human-to-human transmission of HPAI H5N1 viruses. In fact the human-to-human transmission has not been found frequently. Acquisition of Neu5Acα2-6 recognition by mutations in HA would allow the virus to propagate more efficiently in the upper respiratory tract, resulting in spread of the viruses by sneezing and coughing. However, a contradictory observation with SA-linkage expression has been reported. Although Neu5Acα2-3 linkage was not detected in the nasopharynx using MAA lectin, HPAI H5N1 virus, which recognizes only the Neu5Acα2-3 linkage as a receptor, shows infectivity and replication in live tissue sections [50]. This may be because reactivity of the MAA lectin is limited to certain types of Neu5Acα2-3 containing sialoglycans, but not all types of Neu5Acα2-3 linkage. In the avian digestive tract where avian viruses can replicate efficiently, Neu5Acα2-3 linkages are dominantly expressed [36, 52, 53]. Interestingly, Neu5Gcα2-3 linkage recognized preferentially in horses is also detected in the avian digestive tract, suggesting a possible mechanism of bird-to-horse transmission. In fact, Neu5Gcα2-3 as well as Neu5Acα2-3 residues are present in the horse respiratory tract. Both Neu5Acα2-3 and Neu5Acα2-6 residues are present in the swine respiratory tract [18, 52], supporting the suggestion that the pig is an intermediate host between humans and birds.

Table 3. Distribution of Influenza Virus Receptor

Tissues/Cells	Expression of Sialic Acid Species and Linkages	Viral Infectivity/Virus Replication	Reference
Human respiratory tract			
1. Upper respiratory tissue			
Nasopharynx	Neu5Acα2-6	Human (+), Avian (+)	[50, 51]
Nasal mucosa	Neu5Acα2-6		[48]
Paranasal sinuses	Neu5Acα2-6		[48]
Oropharynx	Neu5Acα2-6		[50, 51]
Bronchus	Neu5Acα2-6	Human (+), Avian (-)	[48]
2. Lower respiratory tissue			
Bronchiole	Neu5Acα2-3/2-6		[48]
Lung: alveolus	Neu5Acα2-3/2-6	Human (+) , Avian (+)	[50, 51]
macrophage	Neu5Acα2-3/2-6	Avian (+)	[50, 51]
3. Airway epithelial cells			
Ciliated cells	Neu5Acα2-3	Human (-) , Avian (+)	[47]
Non-ciliated cells	Neu5Acα2-6	Human (+) , Avian (-)	[47]
4. Bronchial epithelial cells			
Cultured cells	Neu5Acα2-3/2-6	Human (+)	[49]
Avian digestive tract			
1. Intestinal tissue			
Duodenum (duck, chicken)	Neu5Acα2-3		[36, 52]
Jejunum (duck)	Neu5Ac/Neu5Gcα2-3		[36]
Cecum (duck)	Neu5Ac/Neu5Gcα2-3		[36]
Colon (duck)	Neu5Ac/Meu5Gcα2-3	Avian (+)	[36, 52]
Colon (chicken)	Neu5Acα2-3		[36]
2. Colon epithelial cells (chicken and quail)			
Cultured cells	Neu5Acα2-3/2-6	Human (+)	[53]
Avian respiratory tract			
1. Respiratory tissue			
Trachea (quail)	Neu5Acα2-3/2-6		[52]
Trachea (chicken)	Neu5Acα2-3/2-6		[52]
Other animal respiratory tract			
1. Respiratory tissue			
Trachea (pig)	Neu5Acα2-3/2-6		[18, 52]
Trachea (horse)	Neu5Ac/Neu5Gcα2-3	Horse (+) (*in vivo*)	[18]

Neu5Acα2-3 and Neu5Acα2-6 expression were determined using MAA (MAA1 and MAA2 in some experiments) and SNA lectins, respectively. Neu5Gcα2-3 was detected using anti-Neu5Gcα2-3Gal antisera. In viral infectivity/virus replication, (+) and (-) indicate observed and not observed, respectively. α 2-3/2-6 indicates the existence of both α2-3 and α2-6 sialic acid linkages. Neu5Ac/Neu5Gc indicates the existence of Neu5Ac and Neu5Gc.

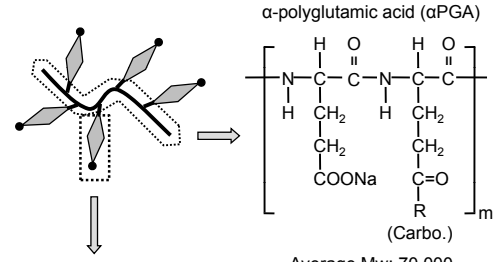
SYNTHETIC GLYCOPOLYMERS WITH MULTIVALENT SIALOGLYCANS

Virus entry inhibitors could enable us to not only address the molecular mechanisms of the virus - host cell interaction, but also control influenza virus infection. A number of such compounds have been developed. For example, glycopolymers carrying multivalent sialylated LacNAc residues have been synthesized as influenza virus inhibitors using polyacrylamide, poly(acrylic acid), and polystyrene as polymer backbones [22, 35, 54-56]. These glycopolymers inhibit the binding of influenza viruses to host cell receptors with much higher affinity than derivatives with monomeric SA. Clustering, ionic charge, and molecular weight of glycans affect the inhibitory activity of SA-glycopolymers on influenza virus infection. Particularly, clustering of LacNAc chains highly contributes to increasing the binding affinity of glycopolymers to viruses. Core carbohydrate length also contributes to interaction of influenza virus HA with Neu5Acα2-6-carrying sugar chains [34]. Neu5Acα2-6 glycan, which spans a wider region on the HA surface, forms a unique umbrella-like conformation. This conformation results in efficient fitting of sialic acid into the RBS. The LacNAc repeats critically influence HA binding contacts in the umbrella-like topology [30].

Generally, synthetic glycopolymers could have several problems for *in vivo* use, such as low solubility, significant cytotoxicity, and immunogenicity. We newly synthesized glycopolymer on α-PGA as the backbone, which showed very low toxicity and high reactivity with influenza virus HA (Fig. **3**). Neu5Acα2-6glycopolymers effectively inhibited human influenza virus infection *in vitro*. Viral infection was markedly reduced by repeating LacNAc residues. Elongation of the core LacNAc units attached to α-PGA enhances the inhibitory activity of glycopolymers because the elongated carbohydrate portion increases binding affinity of glycopolymer with influenza viruses. The results of *in vivo* infection experiments were consistent with those observed *in vitro*. These findings indicated that modification of core carbohydrate chains contributes to enhancement of the binding affinity of sialoglycans with influenza viruses [30, 34]. Addition of LacNAc units may affect clustering of sialoglycans attached to α-PGA.

CONCLUSIONS

Influenza virus characteristically has a diverse range of hosts in nature. The wild birds transmit the virus to other animal species including human. To understand the virus interspecies transmission and epidemic in a certain host, molecular mechanisms on host and tissue tropisms of influenza virus must be elucidated. Viral receptor recognition is considered one of the most crucial factors involved in this tropism. The structures of sialoglycans as receptors are directly related to virus binding specificity and affinity, contributing to the effective interaction between influenza virus and host cells. There are several critical aspects of the virus receptor structure, including SA linkages (α2-3 and α2-6), SA molecular species (Neu5Ac and Neu5Gc), and core carbohydrate determinant and length (LacNAc repeats and Galβ1-4GalNAc). The distribution of specific sialoglycan receptors for distinct influenza viruses may restrict the host range but promote epidemics in a given host. In terms of viral factors, amino acid mutations in HA protein affect binding specificity and affinity of influenza virus to sialoglycans, and finally alter tissue and host tropism. These mutations also enable the virus to adapt to different hosts, resulting in effective transmission in a certain host.



n=1	Neu5Acα2-3 LacNAc
	Neu5Acα2-6 LacNAc
n=2	Neu5Acα2-3 LacNAcβ1-3 LacNAc
	Neu5Acα2-6 LacNAcβ1-3 LacNAc
n=3	Neu5Acα2-3 LacNAcβ1-3 LacNAcβ1-3 LacNAc
	Neu5Acα2-6 LacNAcβ1-3 LacNAcβ1-3 LacNAc

LacNAc, Lactosamine residue (Galβ1-4GlcNAc).
Carbo., Carbohydrate chain.

Fig. (3). Chemical structures of glycopolymers with sialoglycans.α-Polyglutamic acid is the backbone of glycopolymers. R, Carbohydrate chain attached to polyglutamic acid residue of glycopolymer.

In 2009, a new pandemic H1N1 influenza virus originating in swine emerged as an infectious agent in humans. There is a great deal of urgency in the need to control the pandemic influenza virus. Structural and functional information on influenza virus receptors will provide a powerful platform for further research and development of measures to counter the pandemic.

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