Chapter 5
Role of Glycans in Viral Infection

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Abstract A variety of viruses show specific binding to glycans on the cellular surface, such as sialoglycoconjugates, glycosaminoglycans, and histo-blood group antigens. The viral surface proteins recognize terminal sugar chain moieties of glycan and select glycans for binding to specific tissues and hosts. For example, orthomyxoviruses (influenza viruses) and paramyxoviruses recognize terminal moieties of sialic acid linked to galactose for infecting target cells. In most cases, glycans are thought to be involved in cellular surface attachment and cell entry of viruses, as viral receptors and/or coreceptors. Expression of sugar chain moieties is generally dependent on specific tissues, cells, and hosts. Therefore, the specific interactions of viruses with glycans significantly affect tissue tropism and pathogenicity by selection of the viral replication site. For example, human influenza A virus preferentially binds to sialic acid α2,6 linkage to galactose, which is expressed in the human upper respiratory tract. On the other hand, avian influenza A virus preferentially binds to sialic acid α2,3 linkage to galactose, which is expressed in chicken eggs and trachea. The difference in recognition is believed to determine host specificity of influenza A virus. Platforms of the sugar chain are *N*-linked glycan, *O*-linked glycans (containing proteoglycans), and sphingolipid. Difference in these platforms also affects functions of viral receptors. This chapter presents a review about glycans bound and recognized by representative viruses including coronavirus, flavivirus, herpesvirus, norovirus, orthomyxovirus, paramyxovirus, parvovirus, polyomavirus, retrovirus, and reovirus.

Keywords Binding • Heparan sulfate • Histo-blood group antigens • Infection • Glycan • Receptor • Sialic acid • Sugar chain • Sulfatide • Virus

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Abbreviations

AAV	Adeno-associated virus
AAV1	AAV type 1
AAV2	AAV type 2
AAV4	AAV type 4
AAV5	AAV type 5
AAV6	AAV type 6
AAV9	AAV type 9
AIBV	Avian infectious bronchitis virus
ApoE	Apolipoprotein E
BCV	Bovine coronavirus
BKV	BK virus
BPV	Bovine parvovirus
CPV	Canine parvovirus
DEN	Dengue virus
GAG	Glycosaminoglycan
GalCer	Galactosylceramide
HA	Hemagglutinin
HCoV-OC43	Human coronavirus OC43 strain
HCV	Hepatitis C virus
HE	Hemagglutinin-esterase
HN	Hemagglutinin-neuraminidase
HIV	Human immunodeficiency virus
HPAI	Highly pathogenic avian IAV
FPV	Feline parvovirus
hPIV	Human parainfluenza virus
hPIV1	hPIV type 1
hPIV3	hPIV type 3
HSV	Herpes simplex virus
HSV-1	HSV serotype 1
HSV-2	HSV serotype 2
IAV	Influenza A virus
IBV	Influenza B virus
ICV	Influenza C virus
JCV	JC virus
JEV	Japanese encephalitis virus
MHV	Mouse hepatitis virus
MVM	Parvovirus minute virus of mice
MPV	Murine polyomavirus
Neu5Ac	*N*-Acetylneuraminic acid
MuV	Mumps virus
NDV	Newcastle disease virus

Neu5Acα2,3Gal	Neu5Ac α2,3-linked to galactose
$Neu4,5Ac_2$	*N*-Acetyl-4-*O*-acetylneuraminic acid
$Neu5,9Ac_2$	*N*-Acetyl-9-*O*-acetylneuraminic acid
$Neu5,9Ac_2$α2,3Gal	$Neu5,9Ac_2$ α2,3-linked to galactose
$Neu5,9Ac_2$α2,6Gal	$Neu5,9Ac_2$ α2,6-linked to galactose
Neu5Gc	*N*-Glycolylneuraminic acid
NoV	Human norovirus
NSP4	Nonstructural glycoprotein 4
ReV	Reovirus
ReV1	ReV type 1
ReV3	ReV type 3
RoV	Rotavirus
RSV	Human respiratory syncytial virus
SeV	Sendai virus
SV40	Simian virus 40
TGEV	Porcine transmissible gastroenteritis virus
TNF	Tumor necrosis factor
VLP	Virus-like particle
vRNP	Viral ribonucleoprotein complexes
WNV	West Nile virus

5.1 Introduction

All viruses replicate in host cells only and show host (cell) ranges and specificities. Glycans on the cellular surface are highly diverse and species specific. Viral host (cell) ranges and specificities are often dependent on specificity and diversity of glycans on the surface membranes of host cells. In fact, various viruses bind to glycans on the surface membranes of host cells as specific receptors. Typical receptors are sialic acid-containing glycans and sulfated glycans, for example, gangliosides and heparan sulfate, respectively. In many cases, the minus charge of sialic acid and sulfate is likely to play an important role in viral binding with glycans. The typical life cycle of an enveloped virus consists of receptor binding, entry, uncoating of the viral capsid, synthesis of viral components (genomes and proteins), glycosylation of viral proteins, intracellular traffic of viral components, packaging of viral particles, and budding and release of progeny viruses on the cellular surface. Functions of glycans in these steps except for receptor binding mostly remain unknown. This chapter presents a review, mainly in terms of a viral receptor, about glycans recognized by viruses including coronavirus, flavivirus, herpesvirus, norovirus, orthomyxovirus, paramyxovirus, parvovirus, polyomavirus, retrovirus, and reovirus.

5.2 Viruses that Bind to Glycans

5.2.1 Coronavirus

Coronaviruses are positive-stranded RNA viruses and enveloped viruses that are classified within the family *Coronaviridae*. They are a diverse group of viruses that infect various mammalian and avian species. The viruses often affect the respiratory or intestinal tract. It has been shown that many coronaviruses agglutinate erythrocytes (Bingham et al. 1975; Pokorný et al. 1975). Coronaviruses recognize a type of sialic acid as a receptor on cell surface components. Bovine coronavirus (BCV) and human coronavirus OC43 strain (HCoV-OC43) have binding activity to glycoconjugates containing *N*-acetyl-9-*O*-acetylneuraminic acid (Neu5,9Ac_2), through hemagglutinin-esterase (HE) protein and/or spike (S) protein on the viral surface membrane (Schultze et al. 1991a, b; Künkel and Herrler 1993). The HE protein only agglutinates cells that contain a high content of Neu5,9Ac_2 such as mouse and rat erythrocytes (Schultze et al. 1991b). The S protein is able to agglutinate chicken erythrocytes, but the HE protein cannot (Schultze et al. 1991a). Bovine coronavirus is more efficient in recognizing Neu5,9Ac_2 α2,3-linked to galactose (Neu5,9Ac_2α2,3Gal), whereas HCoV-OC43 is superior with respect to Neu5,9Ac_2 α2,6-linked to galactose (Neu5,9Ac_2α2,6Gal) (Krempl et al. 1995). BCV and HCoV-OC43 use Neu5,9Ac_2 as a receptor to initiate infection of cultured cells (Schultze and Herrler 1992; Künkel and Herrler 1993). These viruses also have esterase activity in the HE protein to cleave the 9-*O*-acetyl group of Neu5,9Ac_2, as does influenza C virus (ICV). The esterase activity is believed to help release of progeny viruses from cellular surfaces of host cells. In contrast to most of the coronaviruses, mouse hepatitis virus (MHV) recognizes *N*-acetyl-4-*O*-acetylneuraminic acid (Neu4,5Ac_2) rather than Neu5,9Ac_2 (Regl et al. 1999; Langereis et al. 2012). Receptor recognition of MHV may reflect change in host tropism from other species to mice.

Porcine transmissible gastroenteritis virus (TGEV) and avian infectious bronchitis virus (AIBV) bind to *N*-acetylneuraminic acid (Neu5Ac) α2,3-linked to galactose (Neu5Acα2,3Gal) (Schultze et al. 1992, 1993) via viral S protein. TGEV infects the porcine small intestine, brush border membranes of which express mucin-like and Neu5Ac-rich glycoprotein. Although TGEV uses aminopeptidase N as the main cellular receptor, TGEV S protein may support viral attachment to the brush border membranes (Schwegmann-Wessels and Herrler 2008). TGEV also recognizes *N*-glycolylneuraminic acid (Neu5Gc) (Schultze et al. 1996), which is expressed in pigs (Suzuki et al. 1997). S protein of AIBV shows much higher binding activity to Neu5Acα2,3Gal than does that of TGEV. AIBV uses only Neu5Ac as the main cellular receptor (Winter et al. 2006; Shahwan et al. 2013). AIBV Beaudette strain shows binding activity to heparan sulfate (HS). This virus is an embryo-adapted virus that has the extended tropism in cell culture. HS may in part contribute to extended tropism of AIBV Beaudette strain (Madu et al. 2007) (Table 5.1).

Table 5.1 Binding activities of coronaviruses to glycans

Virus	Glycan (references)
BCV	Neu5,9Ac_2α2,3Gal (Krempl et al. 1995; Künkel and Herrler 1993; Schultze et al. 1991a, b)
HCoV-OC43	Neu5,9Ac_2α2,6Gal (Krempl et al. 1995; Künkel and Herrler 1993; Schultze et al. 1991a, b)
MHV	Neu4,5Ac_2 (Langereis et al. 2012; Regl et al. 1999)
TGEV	Neu5Acα2,3Gal (Schultze et al. 1993; Schwegmann-Wessels and Herrler 2008)
	Neu5Gc (Schultze et al. 1996)
AIBV	Neu5Acα2,3Gal (Schultze et al. 1992, 1993; Shahwan et al. 2013; Winter et al. 2006)
	HS (Madu et al. 2007)

5.2.2 Flavivirus

Flaviviruses are positive-stranded RNA viruses and enveloped viruses that are classified within the family *Flaviviridae*. Dengue virus (DEN) is the most important mosquito-mediated human pathogen. Clinical manifestations of the virus range from a simple self-limited febrile illness known as dengue fever to a hemorrhagic fever and potentially fatal hemorrhagic shock syndrome. All serotypes (1–4) of DEN recognize nLc_4Cer (Galβ1,4GlcNAcβ1,3Galβ1,4Glc1,1'Cer) from mammalian cells (Aoki et al. 2006). DEN type 2 also recognizes Ar_3Cer (GlcNAcβ1,3Manβ1,4Glcβ1,1'Cer) from mosquito cells (Wichit et al. 2011). It is thought that neutral glycosphingolipids share the important determinant for DEN binding and that the β-GlcNAc residue may play a key role in DEN binding. Chemically synthesized derivatives carrying multiple carbohydrate residues of nLc_4 inhibit binding of DEN type 2, indicating that a binding inhibitor based on nLc_4 could be as a potential DEN drug (Aoki et al. 2006). DEN also binds to some glycosaminoglycans (GAGs) such as HS (Chen et al. 1997; Watterson et al. 2012), heparin (Marks et al. 2001), fucoidan (Hidari et al. 2008), and chondroitin sulfate E (Kato et al. 2010) through the virus envelope E glycoprotein, but does not bind to chondroitin sulfates A, B, C, and D or hyaluronic acid (Kato et al. 2010). DEN infection is inhibited by some GAGs such as heparin (Marks et al. 2001), fucoidan (Hidari et al. 2008), and chondroitin sulfate E (Kato et al. 2010). Most GAGs include GlcA and sulfated GlcA. 3-*O*-Sulfated GlcA inhibits DEV infection, but 2-*O*-sulfated and 3,6-di-*O*-sulfated ones do not (Hidari et al. 2012). It is thought that 3-*O*-GlcA is in part a key structure in DEN binding to GAGs. DEN causes leakage of the vascular endothelium, resulting in dengue hemorrhagic fever. Human endothelial cells are highly susceptible to infection by DEN. The susceptibility may be attributed to DEN attachment directed to HS-containing proteoglycan receptors on endothelial cells (Dalrymple et al. 2011). Two encephalitis flaviviruses, Japanese encephalitis virus (JEV) and West Nile virus (WNV), have a binding activity to heparin (Lee et al. 2004). JEV also binds to and is inhibited by HS (Su et al. 2001).

The binding affinity of WNV and JEV for GAG has been suggested to be a determinant for the neuroinvasiveness of encephalitic flaviviruses (Lee et al. 2004).

E1 and E2 envelope glycoproteins of hepatitis C virus (HCV) recognize HS through an important structure such as 6-*O*-sulfation and *N*-sulfation, not through simple ionic interactions (Barth et al. 2003; Kobayashi et al. 2012). Since HCV strongly binds to HS from liver tissues, HS appears to be one of the molecules that confer the liver-specific tissue tropism of HCV infection (Kobayashi et al. 2012). Binding of HCV to the cell surface is not markedly inhibited by heparin, different from other flaviviruses such as DEN and JEV. Cellular HS may act as an alternative receptor for HCV, not a primary receptor (Heo 2008). However, chondroitin sulfate E from squid cartilage strongly interacts with both E1 and E2 proteins and inhibits the entry of pseudotype HCV into cells, suggesting that chondroitin sulfate E is a potential candidate of an anti-HCV drug (Kobayashi et al. 2012). Apolipoprotein E (ApoE), which has a heparin-binding activity, mediates HCV attachment to the cell surface through specific interactions with cellular HS (Jiang et al. 2012). Syndecan-1, which is a core protein to form HS proteoglycans, serves as the major receptor protein for HCV attachment to cells (Shi et al. 2013).

Sulfated GAGs (especially HS) may serve as receptor proteoglycans for the attachment of flaviviruses to target cells. Elucidation of the mechanism by which flaviviruses bind to sulfated GAGs would contribute to the discovery and development of anti-flavivirus drugs (Table 5.2).

5.2.3 Herpesvirus

Herpesviruses are double-stranded linear DNA viruses and enveloped viruses that are classified within the family *Herpesviridae*. The most common manifestations of herpes simplex virus (HSV) infection are mucocutaneous lesions. The initial contact of HSV serotypes 1 and 2 (HSV-1 and HSV-2) with the cellular surface is

Table 5.2 Binding activities of flaviviruses to glycans

Virus	Glycan (references)
DEN	nLc_4Cer (Aoki et al. 2006)
	Ar_3Cer (Wichit et al. 2011)
	HS (Chen et al. 1997; Watterson et al. 2012)
	Heparin (Marks et al. 2001)
	Fucoidan (Hidari et al. 2008)
	Chondroitin sulfate E (Kato et al. 2010)
JEV	Heparin (Lee et al. 2004)
	HS (Su et al. 2001)
WNV	Heparin (Lee et al. 2004)
HCV	HS (Barth et al. 2003; Kobayashi et al. 2012)
	Chondroitin sulfate E (Kobayashi et al. 2012)

Table 5.3 Binding activities of herpesviruses to glycans

Virus	Glycan (references)
HSV-1, 2	HS (especially 3-*O*-sulfated) (Herold et al. 1991; Shukla et al. 1999; Trybala et al. 2000)

believed to be binding of the virus to HS through the viral envelope glycoproteins gB and gC (Herold et al. 1991; Trybala et al. 2000). However, interactions of gB and gC with HS are not sufficient for HSV entry into cells. After adsorption of HSV with HS on the cellular surface, cell entry requires engagement of the viral envelope glycoprotein gD with one of three classified coreceptors, herpesvirus entry mediator, tumor necrosis factor (TNF) receptor family, and immunoglobulin superfamily (Spear et al. 2000). Additionally, 3-*O*-sulfation of glucosamine residues in HS generated by multiple D-glucosaminyl 3-*O*-sulfotransferase isoforms is a key determinant of the gD binding site. HSV-1 cell entry requires interactions of gD with 3-*O*-sulfated HS or other coreceptors described above (Shukla et al. 1999). 3-*O*-Sulfated HS appears to play an important role in HSV-1 entry into many different cell lines (O'Donnell et al. 2010). The glycoprotein gB has a sequence of a putative fusion activity, suggesting that interactions of gB with cellular surface molecules allow the fusion process for cell entry. However, HS-deficient cells are susceptible to HSV-1 infection (Banfield et al. 1995). HSV-1 bearing gB lacking an HS binding site also maintains cell infectivity (Laquerre et al. 1998). Soluble gB, which was generated by a baculovirus protein expression system, also binds to HS-deficient cells and inhibits HIV-1 infection (Bender et al. 2005). Interaction of gB with other molecules except HS may play an important role in HSV-1 infection. 3-*O*-Sulfated HS and HS-binding peptide have been investigated as anti-HSV agents (Copeland et al. 2008; Ali et al. 2012) (Table 5.3).

5.2.4 Norovirus

Human noroviruses (NoVs) are single-stranded positive-sense RNA viruses and small, round, non-enveloped viruses with a diameter of 38 nm that are classified within the family *Caliciviridae*. These viruses are the major causative pathogens of acute viral gastroenteritis characterized by severe diarrhea. NoV virus-like particles (VLPs) bind to histo-blood group antigens demonstrating A, B, and O phenotypes, through the P domain of viral capsid protein, VP1 (Harrington et al. 2002; Marionneau et al. 2002; Chen et al. 2011). For example, the VLPs derived from Norwalk/68 strain bind to H1 antigen (Fucα1,2Galβ1,3GlcNAc; O phenotype), H2 antigen (Fucα1,2Galβ1,4GlcNAc; O phenotype), Le^b antigen [Fucα1,2Galβ1,3(Fucα1,4) GlcNAc], A1 antigen [GalNAcα1,3(Fucα1,2)Galβ1,3GlcNAc; A phenotype], and A2 antigen [GalNAcα1,3(Fucα1,2)Galβ1,4GlcNAc; A phenotype] but not to B1 antigen [Galα1,3(Fucα1,2)Galβ1,3GlcNAc, B phenotype] or B2 antigen [Galα1,3(Fucα1,2)Galβ1,4GlcNAc, B phenotype] (Harrington et al. 2002;

Table 5.4 Binding activities of noroviruses to glycans

Virus	Glycan (references)
NoV	ABH and Lewis antigens in human blood (Harrington et al. 2002; Marionneau et al. 2002)

Huang et al. 2003, 2005; Hutson et al. 2003; Lindesmith et al. 2003). Humans with O phenotype, but not those with B phenotype, are susceptible to NoV Norwalk/68 strain infection (Hutson et al. 2002; Lindesmith et al. 2003). These studies suggested that histo-blood group antigens are receptors of NoV. However, other NoV VLPs display different ABH and Lewis carbohydrate-binding profiles (Harrington et al. 2002; Huang et al. 2005; Shirato et al. 2008; Shirato-Horikoshi et al. 2007). Indeed, Rockx's epidemiological research indicated that some NoVs can infect individuals with different ABH phenotypes (Rockx et al. 2005). For example, VLPs derived from BUDS strain bind to A and B antigens but not to H antigens. The binding activities of NoVs to histo-blood group antigens vary greatly in a strain-dependent manner. NoVs include at least 36 genotypes in VP1 nucleotide sequence. Various genotype NoVs appear to infect humans with any blood types through binding combinations of some histo-blood group antigens (Table 5.4).

5.2.5 Orthomyxovirus

Representative orthomyxoviruses are influenza A virus (IAV), influenza B virus (IBV), and ICV, which are classified within the family *Orthomyxoviridae*. Influenza viruses are enveloped viruses with a diameter of 100 nm and are respiratory pathogens with strong infection spread. IAVs and IBVs are eight-segmented single-stranded negative-sense RNA viruses, and ICVs are seven-segmented single-stranded negative-sense RNA viruses. Viral hosts are wide species including humans, pigs, birds, and horses for IAVs and mainly humans for IBVs and ICVs. Host receptors on the cellular surface membrane are sialic acid residues existing at the terminal position of glycoconjugates, Neu5Ac for IAVs and IBVs and Neu5,9Ac_2 for ICVs (Rogers et al. 1986; Suzuki et al. 1992). IAVs and IBVs have sialidase activity (an enzyme cleaving Neu5Ac from glycoconjugates), and ICVs also have esterase activity (an enzyme cleaving 9-*O*-acetyl group from Neu5,9Ac_2) to prevent trapping of progeny viruses to sialic acid residues on the cellular surface and on viral glycoproteins. These receptors containing sialic acids are thought to be gangliosides and/or *N*-glycans (Suzuki 1994; Chu and Whittaker 2004). In general, human IAVs show preferential binding to Neu5Acα2,6Gal linkage, whereas avian IAVs show preferential binding to Neu5Acα2,3Gal linkage. Swine IAVs bind to both Neu5Acα2,3Gal and Neu5Acα2,6Gal linkages, equally or with predominance toward Neu5Acα2,6Gal linkage (Ito et al. 1997a; Suzuki et al. 1997). IBVs show preferential binding to Neu5Acα2,6Gal linkage (Suzuki et al. 1992). IAVs and IBVs strongly recognize Neu5Acα2,6(or 3)Galβ1,3GlcNAc and Neu5Acα2,6(or 3)

Galβ1,4GlcNAc through interactions of the viral surface glycoprotein, hemagglutinin (HA) (Suzuki et al. 1992, 2000; Suzuki 1994). The human trachea predominantly expresses Neu5Acα2,6Gal linkage (Baum and Paulson 1990). The pig trachea expresses both Neu5Acα2,3Gal and Neu5Acα2,6Gal linkages (Suzuki et al. 1997, 2000). Chicken eggs and trachea express Neu5Acα2,3Gal linkage (Ito et al. 1997b; Abd El Rahman et al. 2009). Glycoconjugates recognized by respective IAVs coincide with respective virus replication sites expressing their glycoconjugates, strongly suggesting that their glycoconjugates are receptors of IAVs. Some H5N1 highly pathogenic avian IAVs (HPAIs) and H7N9 avian IAVs, isolated from humans, show increased binding activity to Neu5Acα2,6Gal linkage (Yamada et al. 2006; Watanabe et al. 2013; Zhang et al. 2013). Acquisition of Neu5Acα2,6Gal linkage binding activity of H5N1 HPAIs is one of the factors that lead to airborne transmission among ferrets (human infection and transmission model) (Imai et al. 2012; Herfst et al. 2012). Increased binding activity of avian IAVs and animal IAVs other than human IAVs to Neu5Acα2,6Gal linkage could cause a pandemic of a new subtype of IAV among humans. As an alternate pandemic mechanism, a new subtype of IAV could arise by genetic reassortment among segmented viral RNAs from simultaneous infections of human and avian IAVs in pigs, which express both Neu5Acα2,3Gal and Neu5Acα2,6Gal linkages in the trachea. In this way, Neu5Ac binding properties of IAVs may be involved in the pandemic occurrence of a new subtype of IAV.

Since 2008, it has been reported that some IAVs, 2009 pandemic H1N1 IAVs and avian IAVs including H5, H6, H7, and H9 subtypes, show preferential binding to 6-sulfo sialyl Lewis X. These IAVs appear to recognize terminal tri- or tetra-oligosaccharides [Neu5Acα2,3Galβ1,4(6-*O*-SO_3H)GlcNAc and Neu5Acα2,3Galβ1,4(Fucα1,3)(6-*O*-SO_3H)GlcNAc] of 6-sulfo sialyl Lewis X (Gambaryan et al. 2008, 2012; Childs et al. 2009).

Major sialic acids are classified into two types: Neu5Ac and Neu5Gc. Almost all equine IAVs show strong preferential binding to Neu5Gc α2,3-linked to galactose (Neu5Gcα2,3Gal) (Ito et al. 1997a; Suzuki et al. 2000). Almost all avian IAVs also show binding activity to one, although Neu5Gc binding activity is weaker than their Neu5Ac binding activity (Ito et al. 1997a, 2000). Some human and swine IAVs show binding activity to Neu5Gc (preferentially to Neu5Gcα2,6Gal linkage) (Suzuki et al. 1997; Masuda et al. 1999; Takahashi et al. 2009). Neu5Gc and Neu5Gcα2,3Gal linkage is expressed in the horse trachea, duck intestine, and pig trachea, which are natural replication sites of IAVs (Suzuki et al. 1997, 2000; Ito et al. 2000). The function of Neu5Gc is predicted to be an IAV receptor, like Neu5Ac. There is a possibility that human and avian IAVs facilitate transmission to pigs through interactions with Neu5Gc. As described above, pigs are potential intermediate hosts that produce a new subtype of IAV between human IAV and avian IAV. Neu5Gc binding properties of these IAVs may also be involved in a pandemic occurrence.

Sulfatide is a 3-*O*-sulfated galactosylceramide (GalCer). IAV specifically binds to sulfatide, even though it does not contain any sialic acids (Suzuki et al. 1996). Sulfatide is not an IAV receptor for initial infection, different from sialic acids.

Table 5.5 Binding activities of orthomyxoviruses to glycans

Virus	Glycan (references)
Human IAV	Neu5Ac (Neu5Gc) α2,6Gal (Masuda et al. 1999; Suzuki et al. 1992; Suzuki 1994; Takahashi et al. 2009)
Avian IAV	Neu5Ac (Neu5Gc) α2,3Gal (Ito et al. 1997a, 2000; Suzuki et al. 1992; Suzuki 1994)
Swine IAV	Neu5Acα2,6Gal (Suzuki et al. 1997)
	Neu5Ac (Neu5Gc) α2,3Gal (Suzuki et al. 1997)
Equine IAV	Neu5Gcα2,3Gal (Ito et al. 1997a; Suzuki et al. 2000)
IAV	6-Sulfo sialyl Lewis X (Gambaryan et al. 2008, 2012; Childs et al. 2009)
	Sulfatide (Suzuki et al. 1996; Takahashi et al. 2008, 2010, 2013a, b)
IBV	Neu5Acα2,6Gal (Suzuki et al. 1992)
ICV	Neu5,9Ac_2 (Rogers et al. 1986; Suzuki et al. 1992)

Caspase-3-dependent apoptosis enhances IAV replication through enhancement of nuclear export of viral ribonucleoprotein complexes (vRNP) (Wurzer et al. 2003). Sulfatide has interacted with newly synthesized HA transferred to the surface membranes of infected cells. The interaction of HA with sulfatide facilitates formation and replication of progeny virus particles through enhancement of nuclear export of vRNP by inducing caspase-3-independent apoptosis (Takahashi et al. 2008, 2010, 2013b). The binding mechanism of the HA ectodomain with sulfatide is thought to be different from that with Neu5Ac (Takahashi et al. 2013a). An inhibitor of HA binding with sulfatide would become a novel drug that inhibits formation of IAV particles and IAV replication. Sulfatide is involved in various biological properties such as the immune system, nervous system, kidney functions, insulin control, hemostasis/thrombosis, cancer, and other microbes (Takahashi and Suzuki 2012). Further study on sulfatide binding of IAVs would contribute to elucidation of these biological mechanisms and diseases associated with sulfatide (Table 5.5).

5.2.6 Paramyxovirus

Paramyxoviruses are single-stranded negative-sense RNA viruses and enveloped viruses with a diameter of 150–250 nm that are classified within the family *Paramyxoviridae*. Some paramyxoviruses have the envelope glycoprotein, hemagglutinin-neuraminidase (HN), displaying both sialic acid binding activity and sialidase activity. Such viruses that infect humans are human parainfluenza virus (hPIV) and mumps virus (MuV), which are members of the genus *Respirovirus* and *Rubulavirus*, respectively. hPIVs [mainly type 1 (hPIV1) and type 3 (hPIV3)] account for 20 % of causative pathogens isolated from children with pneumonia (Sinaniotis 2004). hPIV1 causes most cases of laryngotracheobronchitis (croup) in children, and hPIV type 3 (hPIV3) often causes pneumonia and bronchiolitis

in infants younger than 6 months of age. hPIV1 shows preferential binding to Neu5Acα2,3Galβ1,3GlcNAc (Suzuki et al. 2001; Tappert et al. 2011), whereas hPIV3 shows binding activity to both Neu5Acα2,3Galβ1,3GlcNAc and Neu5Acα2,6Galβ1,3GlcNAc, in addition to Neu5Gcα2,3Galβ1,3GlcNAc. Higher pathogenicity of hPIV3 may be involved in the broader range of receptor recognition than that of hPIV1. Interestingly, both hPIVs strongly bind to oligosaccharides containing branched *N*-acetyllactosaminoglycans (Suzuki et al. 2001). Blood group I-type polylactosamine antigens may be major receptors of hPIVs. Also, HS binding of hPIV3 suggests that HS may play an important role in cell entry of hPIV3 (Bose and Banerjee 2002). On the other hand, sulfatide, which binds to hPIV3, inhibits hPIV3 infection and multinucleated syncytial giant cell formation of infected cells through suppression of viral fusion activity (Takahashi et al. 2012). MuV is a causative pathogen of childhood disease manifested by swelling of parotid glands and salivary glands, sometimes accompanied by complications such as aseptic meningitis, meningoencephalitis, and orchitis. MuV also has an HN spike protein, which was shown to be sensitive to the sialidase inhibitor 2-deoxy-2,3-didehydro-*N*-acetylneuraminic acid (Waxham and Wolinsky 1986). However, binding of MuV with sialoglycoconjugates remains unknown.

Sendai virus (SeV) is a highly transmissible animal respiratory virus in mice, hamsters, guinea pigs, and rats. SeV is a member of the genus *Respirovirus* possessing HN. Gangliosides and glycophorin were investigated as host cell receptors for SeV (Markwell et al. 1981; Hansson et al. 1984; Suzuki et al. 1985; Wybenga et al. 1996). SeV recognizes ganglio-series gangliosides (GD1a, GT1b, and GQ1b) containing the sequence NeuAcα2,3Galβ1,3GalNAc as viral receptors (Markwell et al. 1981). SeV shows preferential binding to neolacto-series gangliosides containing Neu5Acα2,3Galβ1,4GlcNAc, especially branched blood group I-type and/or linear i-type gangliosides (Suzuki et al. 1985). SeV can also bind to bovine erythrocyte glycoprotein GP-2 containing blood group I-type branched polylactosamine oligosaccharides with Neu5Gcα2,3Gal (Suzuki et al. 1983, 1984). Neu5Gc is expressed in animals other than humans (genetically lacking an active enzyme for synthesis of Neu5Gc in humans). SeV can utilize both species of sialic acid Neu5Ac and Neu5Gc to infect animals.

Newcastle disease virus (NDV) is a transmissible pathogen of bird disease and sometimes of mild conjunctivitis and influenza-like symptoms for human infection. NDV is a member of the genus *Avulavirus* possessing HN. NDV shows preferential binding to gangliosides such as sialylparagloboside (IV^3Neu5Acα-nLc_4Cer or IV^3Neu5Gcα-nLc_4Cer) containing Neu5Acα2,3Galβ1,4GlcNAc or Neu5Gcα2,3Galβ1,4GlcNAc and GM3 containing Neu5Acα2,3Gal or Neu5Gcα2,3Gal. NDV also binds to blood group I-type gangliosides, GD3, GM1a, and GD1b, although their binding is weaker than that of sialylparagloboside and GM3 (Suzuki et al. 1985). Gangliosides (GM1, GM2, GM3, GD1a, GD1b, and GT1b) may act as primary receptors, and *N*-linked glycoproteins may function as secondary receptors for NDV entry into cells (Ferreira et al. 2004). On the other hand, pretreatment of chicken East Lansing Line ELL-0 cells with both α2,3- and α2,6-specific sialidases and α2,3(N)- and α2,6(N)-sialyltransferase incubation

Table 5.6 Binding activities of paramyxoviruses to glycans

Virus	Glycan (references)
hPIV1	Neu5Acα2,3Gal (Suzuki et al. 2001; Tappert et al. 2011)
hPIV3	Neu5Acα2,3Gal (Suzuki et al. 2001)
	Neu5Acα2,6Gal (Suzuki et al. 2001)
	Neu5Gcα2,3Gal (Suzuki et al. 2001)
	HS (Bose and Banerjee 2002)
	Sulfatide (Takahashi et al. 2012)
MuV	Sialic acid? (Waxham and Wolinsky 1986)
SeV	Neu5Acα2,3Gal (Suzuki et al. 1985)
	Neu5Gcα2,3Gal (Suzuki et al. 1983, 1984)
NDV	Neu5Acα2,3Gal (Suzuki et al. 1985; Ferreira et al. 2004)
	Neu5Gcα2,3Gal (Suzuki et al. 1985)
RSV	Heparin (Bourgeois et al. 1998; Feldman et al. 1999; Hallak et al. 2000)
	HS (Bourgeois et al. 1998; Feldman et al. 1999; Hallak et al. 2000)
	Chondroitin sulfate B (Hallak et al. 2000)

showed that both α2,3- and α2,6-linked sialic acids containing glycoconjugates may be used for NDV infection (Sánchez-Felipe et al. 2012). Receptor binding properties of NDVs may depend on the viral strain.

Human respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract diseases in infants and young children. RSV is a member of the genus *Pneumovirus* possessing viral surface glycoproteins, attachment G and fusion F proteins, but not including sialidase unlike all paramyxoviruses described above. For virus infection, RSV requires interactions of the G protein and/or the F protein with heparin, HS, and chondroitin sulfate B on the cell surface (Bourgeois et al. 1998; Feldman et al. 1999; Hallak et al. 2000). The G protein and the F protein independently recognize heparin and HS (Feldman et al. 2000). These GAGs and their destroying enzymes also have inhibitory activity against RSV infection (Hallak et al. 2000) (Table 5.6).

5.2.7 Parvovirus

Parvoviruses are non-enveloped viruses that belong to the family *Parvoviridae*. Adeno-associated virus (AAV) is a nonpathogenic human parvovirus with diameters of 20–30 nm. Recombinant AAV has been used for gene transfer to various cells and several organs. AAV type 1 (AAV1), type 4 (AAV4), type 5 (AAV5), and type 6 (AAV6) recognize sialic acids and use them as receptors of infection, but AAV type 2 (AAV2) and type 9 (AAV9) do not. AAV4 specifically recognizes Neu5Acα2,3Gal of *O*-linked glycans, whereas AAV1 and AAV6 specifically recognize both Neu5Acα2,3Gal and Neu5Acα2,6Gal of *N*-linked glycans. Therefore, AAV4 infection is inhibited by mucin that possesses rich *O*-glycans, but AAV1 and

Table 5.7 Binding activities of parvoviruses to glycans

Virus	Glycan (references)
AAV1, AAV6	Neu5Acα2,6Gal (*N*-linked) (Wu et al. 2006)
	Neu5Acα2,3Gal (*N*-linked) (Wu et al. 2006)
AAV2	HS (Summerford and Samulski 1998)
AAV4	Neu5Acα2,3Gal (*O*-linked) (Kaludov et al. 2001)
AAV5	Neu5Acα2,3Gal (Neu5Acα2,6Gal?) (*N*-linked) (Kaludov et al. 2001; Walters et al. 2001)
AAV9	Terminal Gal (*N*-linked) (Shen et al. 2011)
BPV	Neu5Acα2,3Gal (*N*- and *O*-linked) (Johnson et al. 2004)
MVM	Neu5Acα2,3Galβ1,4GlcNAc (Nam et al. 2006)
	Neu5Acα2,8Neu5Ac linkages (Nam et al. 2006)
CPV	Neu5Gc (Löfling et al. 2013)
FPV	Neu5Gc (Löfling et al. 2013)

AAV6 infections are not. AAV5 binds to Neu5Acα2,3Gal of *N*-glycans. Binding of AAV5 to Neu5Acα2,6Gal of *N*-glycans remains unknown. AAV1 efficiently binds to *N*-linked sialylated glycans possessing lactosamine (Galβ1,4GlcNAc) (Walters et al. 2001; Kaludov et al. 2001; Wu et al. 2006). AAV2 infection is strongly or moderately inhibited by heparin or chondroitin sulfate B, respectively. HS mediates AAV2 attachment to the cellular surface and infection (Summerford and Samulski 1998). AAV9 uses the terminal Gal residue of *N*-linked glycans as a receptor (Shen et al. 2011).

Animal parvoviruses sometimes cause fetal diseases for hosts such as dogs and cats. Canine, feline, bovine, and mouse parvoviruses also bind to sialic acids. Bovine parvovirus (BPV) binds to Neu5Acα2,3Gal of both *N*- and *O*-linked glycans for attachment to the cellular surface (Johnson et al. 2004). BPV can strongly bind to glycophorin A through the Neu5Acα2,3Gal moiety of *O*-linked glycans (Blackburn et al. 2005). Parvovirus minute virus of mice (MVM) shows specific binding to terminal moieties, Neu5Acα2,3Galβ1,4GlcNAc such as sialyl Lewis X and Neu5Acα2,8Neu5Ac linkages such as gangliosides GD2, GD3, and GT3 (Nam et al. 2006). Canine parvovirus (CPV) has hemagglutination activity, indicating virus binding to sialic acid (Tresnan et al. 1995). CPV and feline parvovirus (FPV) recognize Neu5Gc but not Neu5Ac. However, Neu5Gc on the cellular surface is unlikely to be a receptor for CPV and FPV infections because overexpression of Neu5Gc has no effect on virus infectivities of some cell lines (Löfling et al. 2013) (Table 5.7).

5.2.8 Polyomavirus

JC virus (JCV) and BK virus (BKV) are non-enveloped viruses with diameters of 40–45 nm that are classified within the family *Polyomaviridae*, closely related to simian virus 40 (SV40) and murine polyomavirus (MPV). Initial JCV infection is

Table 5.8 Binding activities of polyomaviruses to glycans

Virus	Glycan (references)
BKV	Neu5Acα2,3Gal (*N*-linked) (Dugan et al. 2005, 2007)
JCV	Neu5Acα2,6Gal (strong binding, *N*-linked) (Komagome et al. 2002; Liu et al. 1998)
	Neu5Acα2,3Gal (gangliosides) (Komagome et al. 2002)
	LSTc (the strongest binding) (Neu et al. 2010)
MPV	Neu5Acα2,3Gal? (GD1a and GT1b) (Tsai et al. 2003)
SV40	Neu5Acα2,3Gal? (GM1) (Tsai et al. 2003)

thought to occur in childhood and not to cause symptomatic illness but to be a risk factor for progressive multifocal leukoencephalopathy. JCV shows stronger binding to Neu5Acα2,6Gal linkage (of *N*-linked glycans), in addition to binding to Neu5Acα2,3Gal linkage such as gangliosides GM3, GD2, GD3, GD1b, GT1b, and GQ1b, through the major viral capsid protein VP1 (Gee et al. 2004). A linear sialylated pentasaccharide with the sequence LSTc (Neu5Acα2,6Galβ1,4GlcNAcβ 1,3Galβ1,4Glc) binds with JCV and inhibits JCV infection of target cells, strongly suggesting that LSTc is a functional receptor of JCV infection (Neu et al. 2010). JCV binds to an asialoglycolipid, lactosylceramide, but not to GalCer. Therefore, JCV can also bind to GM3 and GD3 after sialidase treatment (i.e., lactosylceramide). JCV weakly binds to GD1a but does not bind to GM1a or GM2 (Liu et al. 1998; Komagome et al. 2002). These studies suggest that both Neu5Acα2,3Gal and Neu5Acα2,6Gal of *N*-linked glycans are also used for cellular surface binding and infection of JCV (Dugan et al. 2008).

BKV infection rarely causes symptom illness in humans but can lead to polyomavirus-associated nephropathy in renal transplant recipients undergoing immunosuppressive therapy. BKV binds to a cellular receptor, Neu5Acα2,3Gal of *N*-linked glycans, via VP1 protein (Dugan et al. 2005, 2007). For nonhuman polyomaviruses, VP1s specifically bind to GD1a and GT1b for MPV and to GM1 for SV40, suggesting that Neu5Acα2,3Gal is a key determinant in the interactions. Gangliosides appear to transport polyoma and SV40 from the cellular surface to the endoplasmic reticulum, and then the viruses enter the nucleus to initiate infection (Tsai et al. 2003) (Table 5.8).

5.2.9 Retrovirus

Retroviruses are single-stranded positive-sense RNA and round enveloped viruses with a diameter of 100 nm that are classified within the family *Retroviridae*. Human immunodeficiency virus (HIV), which is a member of the genus *Lentivirus*, is a pathogen causing long-term and chronic disease that gradually progresses to acquired immunodeficiency syndrome. The viral surface glycoprotein gp120 of HIV binds to some glycolipids containing GalCer (Delézay et al. 1997; Hammache et al. 1998; Harouse et al. 1991), Gb_3Cer (Galα1,4Galβ1,4Glc1,1'Cer) (Mahfoud et al. 2002;

Table 5.9 Binding activities of retroviruses to glycans

Virus	Glycan (references)
HIV	GalCer (Delézay et al. 1997; Hammache et al. 1998; Harouse et al. 1991)
	Gb_3Cer (Lund et al. 2006; Mahfoud et al. 2002)
	GM3 (Hammache et al. 1998)
	Sulfatide (Delézay et al. 1996; van den Berg et al. 1992)
	Heparin (HS?) (Crublet et al. 2008)

Lund et al. 2006), GM3 (Hammache et al. 1998), and sulfatide (Delézay et al. 1996; van den Berg et al. 1992), in addition to heparin (and HS) (Crublet et al. 2008). CD4 is a main primary receptor of HIV for viral attachment to the cellular surface. After interaction of the gp120 with CD4, these glycolipids and HS are thought to interact with gp120 and to act as coreceptors for the fusion process between the cellular membrane and viral membrane of HIV for entry into cells. However, sulfatide may not be a coreceptor for HIV because the fusion process is initiated by mediating binding to GalCer but not to sulfatide (Delézay et al. 1997; Harouse et al. 1991) (Table 5.9).

5.2.10 Reovirus

Reoviruses (ReV) are double-stranded RNA viruses and non-enveloped regular icosahedra non-enveloped viruses with a diameter of 60–80 nm that are classified within the family *Reoviridae*. ReVs can infect the gastrointestinal and respiratory tracts of various mammals. For humans, most children are infected by the age of 5 years. The viral attachment σ1 protein of ReVs recognizes sialic acids of glycoconjugates on the cellular surface. ReV type 1 (ReV1) binds to Neu5Acα2,3Gal and binds strongly to ganglioside GM2, which contains sialic acid linked to the inner galactose residue. The interaction of ReV1 with GM2 is involved in viral infection (Helander et al. 2003; Reiss et al. 2012). ReV type 3 (ReV3) binds to Neu5Acα2,3Gal, Neu5Acα2,6Gal, and Neu5Acα2,8Neu5Ac linkages, in addition to $Neu4,5Ac_2$ (Gentsch and Pacitti 1987; Reiter et al. 2011). Interactions of ReV with sialic acids are believed to act for cellular surface attachment of ReV by rapid but low-affinity adhesion, followed by transition to a higher affinity interaction with an unidentified receptor for cell entry. Therefore, sialic acid is considered to be a coreceptor rather than a main receptor for ReV infection (Barton et al. 2001). ReV1 spreads to the central nervous system via a hematogenous route and infects ependymal cells in the brain, leading to nonlethal hydrocephalus. In contrast, ReV3 spreads to the central nervous system via neural and hematogenous routes and infects neurons, causing lethal encephalitis. These serotype-dependent differences in tropisms and pathogenesis are thought to be involved in the distinct binding with glycochain moieties.

Rotavirus (RoV) is a member of the genus *Rotavirus* and the most important pathogen of severe gastroenteritis in children. There are two groups of RoV in the hemagglutination activity of erythrocytes and sialidase sensitivity of viral infection: sialic acid-dependent and sialic acid-independent RoVs (Isa et al. 2006). A few animal RoVs are sialic acid dependent on the interactions of the viral surface spike VP8* protein, which is formed from the viral VP4 protein by proteolytic cleavage, with sialic acids, whereas human RoVs and the majority of animal RoVs are sialic acid independent. For cell entry, sialic acid-dependent RoVs require gangliosides containing Neu5Ac and/or Neu5Gc, such as GM1(a), GM2, GM3, GD1a, GD1b, GD3, and GT1b, which can inhibit RoV infection (Guo et al. 1999; Martínez et al. 2013; Rolsma et al. 1998; Superti and Donelli 1991; Yu et al. 2012). In addition, some sialic acid-independent RoVs, such as Wa and KUN strains, bind to GM1(a) containing internal Neu5Ac, which can also inhibit infections of these viruses (Guo et al. 1999; Haselhorst et al. 2009; Martínez et al. 2013). These studies suggest that sialic acid-dependent RoVs bind to gangliosides containing terminal Neu5Ac, whereas sialic acid-independent RoVs bind to gangliosides containing internal Neu5Ac. The VP8* protein of human sialic acid-independent RoVs also recognizes histo-blood group antigens, trisaccharide GalNAcα1,3(Fucα1,2)Gal of A antigen for HAL1166 P[11] viral genotype strain (Hu et al. 2012), H1 antigen for P[4] and P[8] viral genotypes, and Le^b antigen for the P[6] viral genotype (Huang et al. 2012). The interactions of RoVs with sialo- or asialo-receptors are dependent on viral strains and genotypes. Nonstructural glycoprotein 4 (NSP4) encoded by RoVs is believed to function as an enterotoxin. NSP4 is secreted as an oligomeric lipoprotein from infected cells and binds to sulfated GAGs (Didsbury et al. 2011). Thus, glycans appear to be involved in the infection and pathogenesis of RoVs and NSP4 through cellular surface attachment (Table 5.10).

Table 5.10 Binding activities of reoviruses to glycans

Virus	Glycan (references)
ReV1	Neu5Acα2,3Gal (Helander et al. 2003)
	GM2 (Reiss et al. 2012)
ReV3	Neu5Acα2,3Gal (Reiter et al. 2011)
	Neu5Acα2,6Gal (Reiter et al. 2011)
	Neu5Acα2,8Neu5Ac (Reiter et al. 2011)
	$Neu4,5Ac_2$ (Gentsch and Pacitti 1987)
RoV	Gangliosides (Neu5Ac and/or Neu5Gc) (Guo et al. 1999; Martínez et al. 2013; Rolsma et al. 1998; Superti and Donelli 1991; Yu et al. 2012)
	Histo-blood group A1 antigen (Hu et al. 2012)
	Histo-blood group H1 antigen (Huang et al. 2012)
	Histo-blood group Le^b antigen (Huang et al. 2012)
RoV NSP4	Sulfated GAGs (Didsbury et al. 2011)

5.3 Conclusion

A variety of viruses recognize glycans such as sialoglycoconjugates, GAGs, and histo-blood group antigens. These glycans are often thought to serve as receptors and/or coreceptors for cellular surface attachment and cell entry of viruses and viral toxins. The interactions of viruses with glycans determine virus-dependent tissue tropism, host, and pathogenicity. In rare cases, the interaction of IAV HA with sulfatide functions as a start switch of progeny virus particle formation, not as a receptor for IAV infection. It may be important to evaluate the interactions of viruses with glycans in terms of insights different from a receptor function. Further studies combining virology and glycobiology should lead to the elucidation and discovery of novel infection and replication mechanisms of a variety of viruses.

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