Cell. Mol. Life Sci. 63 (2006) 1331–1354
1420-682X/06/121331-24
DOI 10.1007/s00018-005-5589-y

Cellular and Molecular Life Sciences

Review

Sialic acid-specific lectins: occurrence, specificity and function

F. Lehmann[a, *], E. Tiralongo[b] and J. Tiralongo[a]

[a] Institute for Glycomics, Griffith University (Gold Coast Campus), PMB 50 Gold Coast Mail Centre Australia 9726 (Australia), Fax: +61 7 5552 8098; e-mail: f.lehmann@griffith.edu.au
[b] School of Pharmacy, Griffith University (Gold Coast Campus), PMB 50 Gold Coast Mail Centre Australia 9726 (Australia)

Received 13 December 2005; received after revision 9 February 2006; accepted 15 February 2006
Online First 5 April 2006

Abstract. Sialic acids consist of a family of acidic nine-carbon sugars that are typically located at the terminal positions of a variety of glycoconjugates. Naturally occurring sialic acids show an immense diversity of structure, and this reflects their involvement in a variety of biologically important processes. One such process involves the direct participation of sialic acids in recognition events through specific interactions with lectins, a family of proteins that recognise and bind sugars. This review will present a detailed overview of our current knowledge regarding the occurrence, specificity and function of sialic acid-specific lectins, particularly those that occur in viruses, bacteria and non-vertebrate eukaryotes.

Keywords. Sialic acid, lectin, sialoglycoconjugate, sialic acid-specific lectin, adhesin, infectious disease, immunology.

Introduction

Sialic acids (Sia) are a family of nine-carbon α-keto acids (Fig. 1) found predominantly at the non-reducing end of oligosaccharide chains on glycoproteins and glycolipids. Sia can occur free in nature, but are generally found glycosidically linked to either the 3- or 6-hydroxyl group of galactose (Gal) residues or to the 6-hydroxyl group of *N*-acetylglucosamine (GlcNAc) or *N*-acetylgalactosamine (GalNAc) residues. Sia can also exist as α2,8-linked homopolymers known as polysialic acid (Fig. 1). The expression of Sia was previously thought to be unique to deuterostomes and pathogenic bacteria infecting these animals; however, more recent findings suggest that they may be more widely distributed and possibly quite ancient in their origin [1, 2].

Sia show remarkable structural diversity, with the family currently comprising over 50 naturally occurring members [1, 2]. The largest structural variations of naturally occurring Sia are at carbon 5, which can be substituted with either an acetamido, hydroxyacetamido or hydroxyl moiety to form 5-*N*-acetylneuraminic acid (Neu5Ac), 5-*N*-glycolylneuraminic acid (Neu5Gc) or deaminoneuraminic acids (KDN), respectively (Fig. 1) [1]. Further structural diversity is generated primarily by a combination of the above-mentioned variations at C-5, with modifications of any of the hydroxyl groups located at C-4, C-7, C-8 and C-9.

The diversity of Sia structure is reflected by its involvement in a variety of biological functions, many stemming from its unique physical and chemical properties, such as charge and size. For those interested in this aspect of Sia biology we recommend several excellent reviews [1–3]. Beside the more general functions attributed to its unique physiochemical properties, Sia can also mediate a variety of specific recognition processes [3]. For instance, as the terminal residues on many glycoconjugates, Sia can mask underlying structures, as observed for erythrocytes and other blood cells, as well as serum glycoproteins, where the

* Corresponding author.

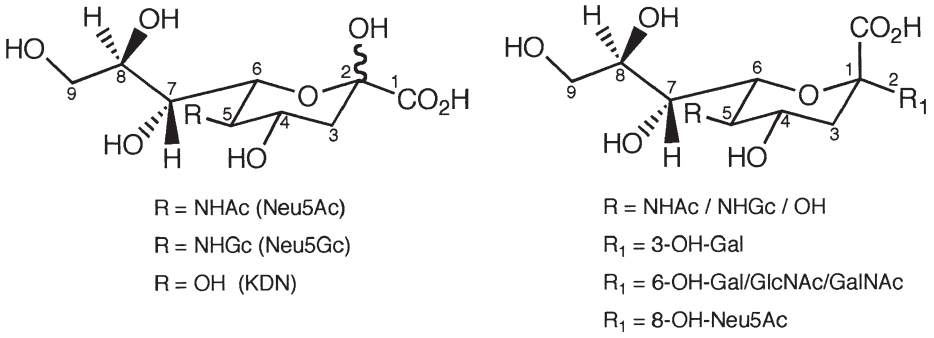

Figure 1. The structural diversity of Sia is generated by a combination of variations at C-5 with modifications of any of the hydroxyl groups at C-4, C-7, C-8 and C-9. Sia is predominantly found glycosidically linked via α2,3-, α2,6- or α2,8-linkages to underlying sugars as shown.

addition of Sia to the subterminal Gal impedes the binding of Gal-specific receptors of macrophages and hepatocytes, hindering their removal from the circulation [4].

In contrast to masking, Sia can also directly participate in a variety of recognition events (Fig. 2), with this probably being its most important role. First noted in microorganisms, Sia are now recognized as being the most common ligand (or receptor) for pathogenic and non-pathogenic viruses, bacteria and protozoa. Obviously, if Sia only served as recognition sites for pathogens, the biosynthesis of such a complex monosaccharide would have been eliminated during evolution in higher animals. However, due to their exposed position on cell surfaces, Sia have evolved not only to shield cells from the environment, but also as recognition markers in multicellular organisms. Sugar-binding proteins (excluding antibodies and enzymes) are collectively called lectins, and there are numerous Sia-specific lectins in nature. This review will present a detailed overview of the occurrence, specificity and function of Sia-specific lectins, particular in viruses, bacteria and non-vertebrate eukaryotes. In all cases, where the crystal structures of Sia-specific lectins have been elucidated, these are cited within the Tables.

Viruses

The adhesion of a virus particle to specific cell-surface molecules is the key interaction between the virus and its host, and as such is a critical step in the development of viral disease, as well as being a potential target for antiviral therapy. Attachment strategies employed by viruses involve multiple interactions between several viral and cellular molecules. Many viruses employ an adhesion-strengthening attachment strategy in which primary virus-cell interactions involve low-affinity adhesion of the virus to common cell surface molecules that are often carbohydrates in nature. This initial phase of attachment is then followed by higher-affinity interactions between the virus and a secondary receptor on permissive cells, an event that often triggers virus entry. Members of at least eight different virus families exploit sialoglycoconjugates for attachment. Some viruses bind preferentially to Sia attached via a particular glycosidic linkage, and this specificity may contribute to virus host range, tissue tropism and pathogenesis.

In this section, we will discuss the role of viral Sia-specific lectins in host cell infection and pathogenesis, specifically Sia-lectins from influenza virus, paramyxovirus, reovirus and picornavirus. A comprehensive list of viral Sia-specific lectins thus far identified is presented in Table 1.

Influenza viruses

Influenza belong to the family Orthomyxoviridae, which show a near obligatory dependence on the host cell surface Sia for infection. Whereas influenza B and C are purely human viruses, influenza A viruses circulate in a wide range of avian and mammalian hosts. Influenza A virus is probably the best-known and most-studied example in the field, and with the recent outbreaks of avian influenza in humans, probably the most likely to cause the next influenza pandemic.

The surface of the influenza virus is decorated with two major antigenic glycoproteins, the receptor-destroying enzyme sialidase and the viral lectin haemagglutinin (HA). Even though HA and sialidase play quite different roles in viral infection, both recognize a common ligand, Sia. For a recent review describing the role of sialidase in influenza virus infection see [5 and references therein]. Work performed by Suzuki *et al*. has demonstrated that the host range variation in influenza virus A is due in part to the type of Sia linkage present on the host cell receptor (reviewed in [5]). Therefore, we will only briefly describe the relevance of the Sia linkage specificity of influenza virus A HA, predominantly as it relates to the H5N1, H9N2 and H7N7 strains of avian influenza virus.

Human influenza A virus HA predominantly binds Neu5Acα2,6Gal structures which are present on non-

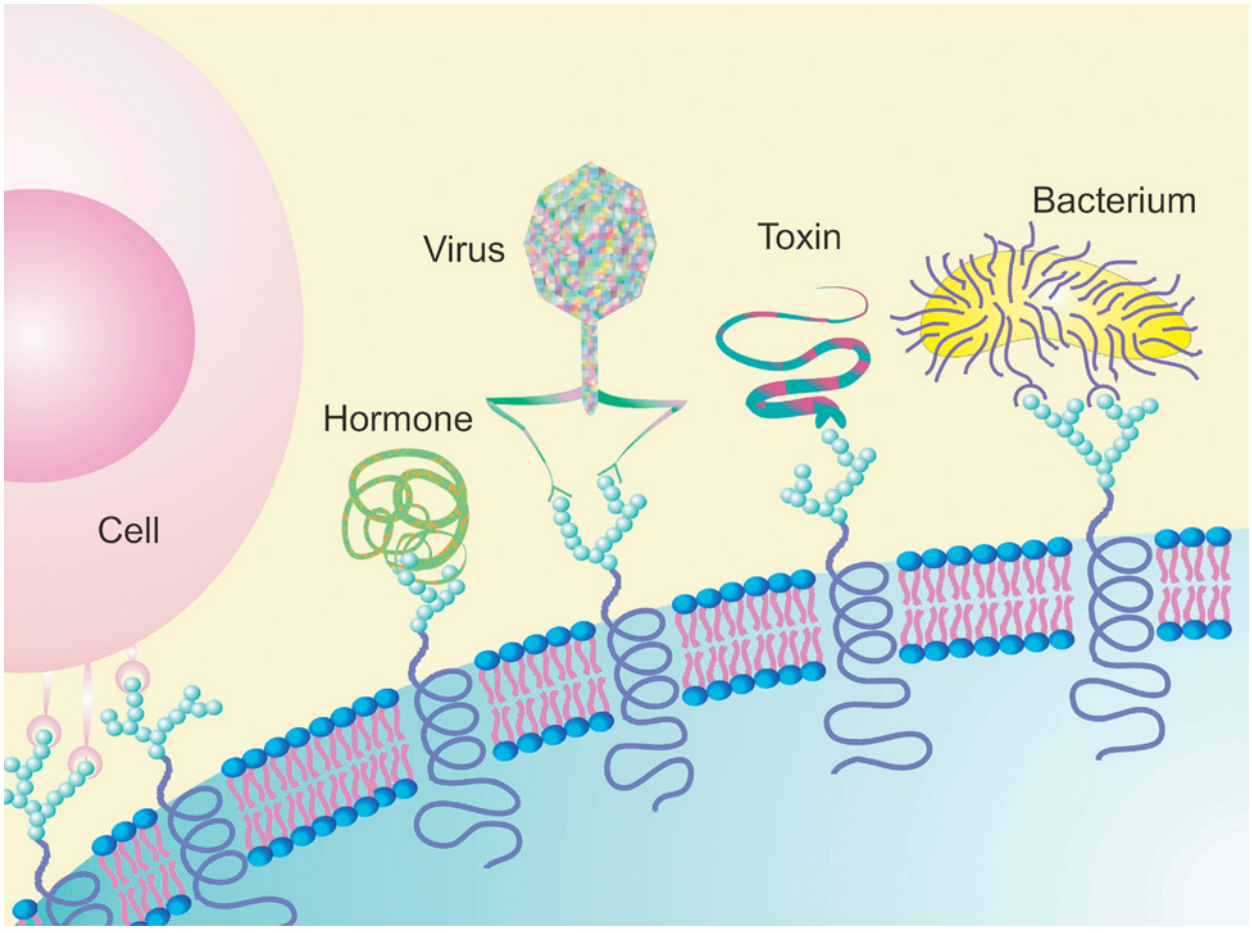

Figure 2. Sia, which frequently occupy the terminal position of glycan chains on glycoproteins (the individual sugars are represented by spheres) or glycolipids, participate in numerous recognition events through Sia-specific lectins. These include, from left to right, cell-cell communication in multicellular organisms and host-pathogen interactions. This figure was provided by Dr. Jenny Wilson from the Institute for Glycomics, Griffith University, Australia.

ciliated cells of the human trachea. The avian influenza virus exclusively binds Siaα2,3Gal, thus limiting the host range to those species possessing these receptor structures (e.g. birds, horses and pigs). Recently, however, ciliated cells of the human trachea were found to contain α2,3-linked Neu5Ac and were able to replicate some avian influenza variants [6]. This finding provides a plausible mechanism accounting for the recent infections and fatalities associated with the H5N1 strain that were acquired only through direct contact with infected birds. The mechanism of H7N7 transmission discovered in the Netherlands is unknown. On the other hand, the H9N2 strain has acquired a preference for α2,6-linked Neu5Ac, therefore potentially being transmissible from human to human [7]. However, H9N2 has only caused mild symptoms in infected individuals, and no cases of human-to-human transmission have been reported. This indicates that an avian influenza virus with HA specificity similar to human strains, therefore allowing human-to-human transmission, is plausible.

The rise of a strain as fatal as H5N1, but potentially as transmissible as H9N2, will largely depend not only on the acquisition of HA human-like receptor specificity, but also on the maintenance of virulence characteristics. The most probable mechanism involves the participation of an intermediate host that can replicate both avian and human viruses, thus acting as a mixing vessel. Pigs represent one such adaptive host, since they possess both α2,3- and α2,6-linkages and have been shown to bind avian and human influenza A viruses [8].

Interestingly, the HA specificity of the Spanish flu, a strain that resulted in 20 million deaths in 1918/19, possesses the binding site specificity of an avian HA [9, 10], but preferentially binds Neu5Acα2,6Gal [11]. The available crystal structure [9, 10], as well as recent binding studies [12], strongly suggests that the exchange of Glu190 in the avian HA with Asp190 in Spanish flu HA leads to a subtle increase in binding pocket size that is then able to accommodate the binding of Neu5Acα2,6Gal structures. This shows that a minor alteration in the binding pocket of

Table 1. Viruses and their Sia-specific lectins.

Species	Lectin[1]	Specificity	3D structure [Ref.]	Ref.
Orthomyxoviridae				
Influenza virus A	HA			[5 and
human		Neu5Acα2,6Gal	[129]	references
avian		Neu5Acα2,3Gal	[130]	therein]
porcine		Neu5Acα2,3Gal, Neu5Acα2,6Gal	[130]	
equine		Neu5Gcα2,3Gal		
Influenza virus B	HA	Neu5Acα2,6Gal	[131]	[14]
Influenza virus C	HE	Neu5,9Ac_2	[132]	[14]
Paramyxoviridae				
Newcastle disease virus	HN	GM3, GM2, GM1,GD1a, GD1b, GT1b *N*-glycans	[19]	[18]
Sendai virus	HN	NeuAcα2,3Galβ1,3GalNac/4GlcNAc		[16]
Human parainfluenza virus type 1	HN	NeuAcα2,3Galβ1,4GlcNAc		[17]
Human parainfluenza virus type 3	HN	NeuAc/Neu5Gca2,3/6Galb1,4GlcNAc	[133]	[17]
Parainfluenza virus 5	HN	Sia	[134]	[15]
Porcine rubulavirus LPM	HN	Neu5Acα2,3Gal		[135]
Mumps virus	HN	Sia		[136]
Polyomaviridae				
Murine polyoma virus	VP1		[137]	[138]
large-plaque		Neu5Acα2,3Galβ1,3GalNA		
small-plaque		Neu5Acα2,3Galβ1,3[Neu5Acα2,6]GalNAc		
Simian virus 40	VP1	GM1		[139]
Human polyoma virus JC		Siaα2,6		[140]
Human polyoma virus BK		Siaα2,3		[141]
Coronaviridae				
Bovine coronavirus	S protein, HE	Neu5,9$Ac_2\alpha$2,3Gal ≥ Neu5,9$Ac_2\alpha$2,6Gal		[22]
Human coronavirus OC43	S protein	Neu5,9$Ac_2\alpha$2,6Gal ≥ Neu5,9$Ac_2\alpha$2,3Gal		[142]
Porcine haemagglutinating encephalomyelitis virus	HA-A	Neu5,9Ac_2		[143]
Porcine transmissible gastroenteritis coronavirus	S protein	Neu5Gcα2,3 ≥ Neu5Acα2,3		[26]
Avian infectious bronchitits coronavirus	HA-A	Neu5Acα2,3		[25]
Murine hepatitis virus	HE	Neu4,5Ac_2		[24]
Reoviridae				
Reovirus type 3	σ1	Sia	[144]	[30]
Reovirus type 1	σ1	Siaα2,3		[32]
Avian rotavirus PO-13, Ty-3, Ty-1, Ch-1	VP4	Sia		[145]
Porcine rotavirus group A OSU	VP4	Neu5Gc-GM3 ≥ Neu5Ac-GM3		[146]
Porcine rotavirus CRW-8	VP4	Sia	[147]	[148]
Porcine rotavirus group C AmC-1	VP4	Sia		[149]
Porcine rotavirus A131, A138, A411, A253, SB-1A, C134, TFR-41, EE, YM	VP4	Sia		[148]
Human rotavirus KUN, MO	VP4	GM1		[150]
Human rotavirus Wa, HCR3a	VP4	Sia		[148]
Rhesus rotavirus	VP4	Neu5Ac > > Neu5Gc	[151]	[37]
Simian rotavirus RRV	VP4	Sia		[152]
Simian rotavirus SA11	VP4	Neu5Gc-GM3		[34]
Simian rotavirus SA11 4F	VP4	Sia		[148]
Bovine rotavirus NCDV	VP4	Neu5Gc-GM3		[34]
Bovine rotavirus UK	VP4	Neu5Ac-GM3, GM1		[34]
Bovine rotavirus RF, BRV033	VP4	Sia		[148]
Canine rotavirus CU-1, K9	VP4	Sia		[148]
Feline rotavirus Cat97	VP4	Sia		[148]
Bluetongue virus		Neu5Ac, Neu5Gc		[153]
Adenoviridae				
Adenovirus type 37	fiber knob	Siaα2,3	[154]	[155]
Adenovirus types 8, 19a	fiber knob	Sia		[155, 156]

Table 1. (Continued).

Species	Lectin[1]	Specificity	3D structure [Ref.]	Ref.
Picornaviridae				
Encephalomyocarditis virus		Sia		[38]
Human rhinovirus 87		Sia		[39]
Theiler's murine encephalomyelitis virus BeAn	VP2	Siaα2,3	[45]	[44]
Mengo encephalomyocarditis virus	HA-A	Sia		[40]
Bovine enterovirus 261		Sia		[41]
Human enterovirus type 70		Siaα2,3		[43]
Hepatitis A virus	VP1/VP3	Sia		[42]
Equine rhinitis A virus		Siaa2,3		[157]
Parvoviridae				
Canine parvovirus	VP2	Sia		[158]
Feline panleukopenia virus		Sia		[158]
Murine minute virus	VP1	Sia		[159]
Bovine parvovirus	HA-A	Neu5Acα2,3Gal		[160]
Adeno-associated virus serotype 4	HA-A	Neu5Acα2,3Gal	[161][2]	[162]
Adeno-associated virus serotype 5	HA-A	Neu5Acα2,3Gal, Neu5Acα2,6Gal	[159][2]	[162]
Papillomaviridae				
Monkey B-lymphotropic papovavirus		Sia		[163]
Rhabdoviridae				
Rabies virus		Sia		[164]
Vesicular stomatitis virus		Sia		[165]
Herpesviridae				
Murine cytomegalovirus		Neu5Ac		[166]
Human cytomegalovirus		Neu5Ac > Neu5Gc		[167]
Hepdnaviridae				
Hepatitis B virus	small S protein	Neu5Ac		[168]

[1] HA, haemagglutinin; HE, haemagglutinin esterase; HN, haemagglutinin neuraminidase; HA-A, haemagglutinin activity observed.
[2] Structure of whole virus determined.

avian HA can increase the host range to include humans, resulting in a potentially pandemic influenza A virus.

The influenza C virus HA is unique among influenza virus HAs in two key ways: (i) it preferentially binds 9-*O*-acetylated Sia, and (ii) it possesses an acetylesterase activity that removes the *O*-acetyl group at C-9 following binding. Due to this ability the influenza C virus HA is referred to as a HA-esterase (HE) with receptor-destroying activity [13]. This unique HA has proved a useful tool for investigating the biology of 9-*O*-acetylated Sia [14].

Paramyxoviruses

Several paramyxoviruses, including Newcastle disease virus (NDV), Sendai virus, parainfluenza virus 5 (SV5), and mumps virus depend on host cell surface Sia for attachment. The attachment protein has HA and sialidase activities that binds to Sia-containing cell surface molecules, and mediates enzymatic cleavage of Sia from the surface of virions and infected cells (reviewed in [15]).

The chemical nature of paramyxovirus receptors has been studied extensively in Sendai virus [16], where gangliosides bearing Neu5Ac on the subterminal Gal, such as GD1a, as well as the glycoprotein glycophorin have been shown to act as receptors. The binding specificity of human parainfluenza viruses types 1 (hPIV1) and 3 (hPIV3) has also been characterized [17]. Whereas hPIV1 preferentially recognizes oligosaccharides containing *N*-acetyllactosaminoglycan branches with terminal Neu5Acα2,3Gal, hPIV3 additionally recognizes Neu5Acα2,6Gal- and Neu5Gcα2,3Gal-containing receptors. A two-phase model, where gangliosides represent the primary receptors and *N*-linked glycoproteins serve as the second receptor critical for viral entry, has been suggested for NDV [18]. Structural analysis of the NDV lectin reveals two different Sia binding sites; however, the second binding site is not essential for viral infection, but probably enhances the fusion promoting activity of the sialidase [19].

Coronaviruses

Human coronaviruses (CoV) cause respiratory tract illnesses such as the common cold and the recently identi-

fied SARS-CoV, which causes a life-threatening pneumonia and represents the most pathogenic human coronavirus identified thus far [20].

Several coronavirus strains, as demonstrated for bovine coronavirus (BCoV), the human coronavirus OC43 (HCoV-OC43) and the porcine haemagglutinating encephalomyelitis virus (HEV), use 9-*O*-acetylated Sia as receptor determinants [21]. Like influenza C, coronaviruses possess a HE. These viruses also express a spike protein (S) on their surface that has greater HA than HE activity and also binds $Neu5,9Ac_2$ [22]. This suggests that after initiating the infection by attachment to host cell surface $Neu5,9Ac_2$, a secondary interaction of the S protein with a specific protein receptor is necessary for activation of the fusion process [23].

Interestingly, analysis of the murine hepatitis virus MHV-S and MHV-JHM strains with free Sia derivatives show that their HE specifically recognizes 4-*O*-acetyl Sia ($Neu4,5Ac_2$) and not $Neu5,9Ac_2$. Since $Neu4,5Ac_2$ has not been found in mice, the nature of the substrates and/or secondary receptors for MHV-S in the natural host remains to be determined [24]. In contrast, avian infectious bronchitis virus (IBV) and the transmissible gastroenteritis virus (TGEV) do not possess genes encoding HE, and instead bind non-acetylated α2,3-linked Sia [25, 26]. This interaction is not only important for enhancing cell attachment and entry, but also increases the stability of the virus against detergent-like bile salts encountered in the gastrointestinal tract [27]. Furthermore, a role in overcoming the mucus barrier and intestinal peristalsis by binding of virions to Sia of mucin-type glycoproteins has been postulated [28].

Reoviruses

Reoviruses belong to the family Reoviridae, which includes the orthoreoviruses, rotaviruses, Colorado tick fever and Bluetongue virus. Within the orthoreoviruses, most serotype 3 viruses bind cell surface Sia. Infections are initiated by the binding of the viral attachment protein, σ1, to receptors on the host cell surface. The σ1 protein consists of two distinct receptor-binding regions, a Sia-binding fibrous tail lectin domain and a junctional adhesion molecule-1 (JAM1)-binding globular head domain [29, 30].

The ability of the σ1 lectin domain to utilize Sia as a viral coreceptor is dictated by a single amino acid, with the exchange of Leu204 to Pro204 converting a Sia negative binding (Sia^-) phenotype to a Sia-positive binding (Sia^+) phenotype [30]. In the case of Sia^+ reovirus strains, initial binding is likely to be via multivalent virion-Sia interactions. By virtue of its rapid association rate, this interaction attaches the virion to the cell surface, enabling it to diffuse laterally until it interacts with the σ1 head receptor molecule. This secondary interaction with JAM1 seems to be the only binding event available to Sia^- strains and may be necessary and sufficient for virus endocytosis [31]. Although serotype 1 reoviruses were initially thought not to bind Sia, recent studies have now shown that α2,3-linked Neu5Ac is involved in reovirus T1L binding to rabbit M cells and polarized $Caco\text{-}2_{BBe}$ cells [32].

Rotaviruses, the leading cause of gastroenteritis in humans, possess an outermost layer composed of two proteins, VP4 and VP7. Treatment of the virus with trypsin results in the specific cleavage of VP4 into the polypeptides denoted as VP8* and VP5*. It is generally accepted that Neu5Ac is required by several animal rotavirus strains to attach to the cell surface. The infectivity of some of these strains is greatly diminished by the treatment of cells with sialidase; consequently, these strains are termed sialidase-sensitive. By contrast, many animal strains and most strains isolated from humans are sialidase-resistant [33]. This is believed to be due to the ability of these strains to bind gangliosides that possess internal Sia that are resistant to sialidase treatment [34]. The gangliosides GM1 and GM3, and the Gal component of glycoprotein receptors, as well as integrins $\alpha2\beta1$ and $\alpha4\beta1$ all play a role in attachment and entry of rotaviruses into host cells, indicating that the rotavirus functional receptor is a complex of several cell components [35]. A recently proposed model suggests that the initial contact of a sialidase-sensitive virus strain with the cell surface is through the binding of the VP8* domain of VP4 to a ganglioside receptor which induces a conformational change in VP4, thus allowing the virus to interact with integrin $\alpha2\beta1$ through VP5*. Following this second interaction, one to three additional interactions take place involving VP5* and VP7, integrins $\alpha v\beta3$ and $\alpha x\beta2$, and probably other proteins [36].

Studies have now demonstrated that the rhesus rotavirus VP8* core specifically binds α-glycosidically linked Sia with a 10-fold lower affinity for Neu5Gc, requires no additional carbohydrate moieties for binding and does not distinguish 3′ from 6′ sialyllactose [37]. The broad specificity and low affinity of Sia binding by VP8* supports the suggestion that more specific interactions that occur after Sia binding are responsible for rotavirus host range and cell-type specificity.

Picornavirus

The Picornaviridae comprise one of the largest and most important families of human and animal pathogens, including hepatitis A virus (HAV) and human rhinovirus (HRV). Among the Picornaviridae the use of Sia as a receptor has been described for encephalomyocarditis virus, human rhinovirus 87 (HRV87), Theiler's murine encephalomyelitis virus (TMEV), mengovirus and bovine enterovirus 261 [38–41]. Moreover, the hepatitis A

virus (HAV) has recently been found to bind human red blood cells through an interaction with sialoglycoproteins [42]. Among the enteroviruses (EV), EV70 is the only human EV requiring cell surface Sia for attachment, with a strong preference for *O*-linked glycans containing terminal Siaα2,3-linked to galactose [43].

TMEV is unique among picornaviruses because of the existence of two naturally occurring neurovirulence groups with distinct disease phenotypes and highly similar amino acid sequences (>90%) and capsid structures [44]. While it is possible that members of the two TMEV neurovirulence groups use the same receptor protein, the attachment factors (co-receptors) clearly differ. While high-neurovirulence strains bind the proteoglycan heparan sulfate, low-neurovirulence strains bind α2,3-linked Sia moieties on *N*-linked oligosaccharides [44]. Site-specific mutations together with crystallographic studies revealed four tightly clustered virus capsid amino acids, all within a positively charged area on the viral surface, with Sia contact through non-covalent hydrogen bonds being important for low-neurovirulence strain central nervous system persistence [45].

Bacteria

As is the case with viral infections, adhesion of bacteria to host tissues represents an initial and essential step in pathogenesis. Bacterial surface components that mediate adherence are collectively called adhesins. Because cell surfaces are decorated with glycoconjugates, it is not surprising that an increasing number of carbohydrate-specific bacterial adhesins have been discovered. Several Gram-negative and Gram-positive bacteria have been reported to use Sia-containing glycoconjugates on host cells as ligands (see Table 2 for full listing), although the identity of the specific bacterial lectin (or adhesin) remains uncertain in many cases. Often, these lectins are associated with multi-subunit fimbriae or pili, with the expression of specific lectins being responsible for the tissue tropism of infections.

Gram-negative bacteria

Escherichia coli

Escherichia coli represents the head of the large bacterial family, Enterobacteriaceae, which are facultative anaerobic rods that live in the intestinal tract of healthy and diseased animals and humans. Pathogenic *E. coli* express several classes of fimbriae-associated lectins that mediate attachment through specific binding to different glycoconjugate receptors on a variety of human cells [46]. Strains shown to use sialoglycoconjugates as attachment sites express either S-fimbriae, K99-fimbriae, the F41 adhesin or one of the colonization factor antigens (CFA) [47].

S-fimbriae were found to preferentially bind to gangliosides carrying Neu5Gcα2,3Gal and Neu5Acα2,8Neu5Ac structures, with the C-8 and C-9 hydroxyl groups on Sia being required for recognition [48]. The adhesion protein, SFaS, a minor component of the multi-subunit S-fimbriae, has been cloned and characterized [47]. Mutagenesis studies suggest that the amino acids Lys116 and Arg118 influence SfaS binding to Sia [49]. Notably, these amino acids are part of a stretch of conserved amino acids which are also found in other bacterial Sia-binding lectins such as CFAI and K99 adhesins of *E. coli* and the *Vibrio cholerae* toxin B subunit, as well as the *E. coli* toxin LTI-B [49].

The K99 fimbrial antigen is often found in enterotoxigenic *E. coli* isolated from calves, piglets and lambs suffering from diarrhoea. In contrast to S-fimbriae, where the adhesin SfaS is only a minor component, in K99-fimbriae the Sia binding site is found in the major subunit. The presence of a hydrophobic region close to the binding site seems to enhance Sia binding affinity [50, 51], which favours Neu5Gc over Neu5Ac. The specific recognition of Neu5GcLacCer by K99-fimbriated *E. coli* might contribute to host specificity, since humans and animals that lack Neu5Gc cannot be infected [52]. Often expressed simultaneously with K99 is F41, which binds glycophorin A with a clear selectivity for the M blood type [53]. Although the binding of F41 to glycophorin is clearly Sia-dependent, the polypeptide must also be involved since the M and N blood type determinant resides in the amino acid composition.

Of the CFA the most extensively studied are CFAI [54], CFAII [55] and CFAIV [56]. Whereas CFAI is a single fimbrial antigen, CFAII and CFAIV are composed of antigenically distinct structures called coli surface antigens. Although very little is known about the receptors or binding structures for the different CFA, CFAI has been shown to bind to free Sia [57], sialoglycoproteins [58] and GM2 [59]. Furthermore, purified CS2 antigen belonging to CFAII has been shown to be a Sia-dependent lectin inhibited specifically by sialyllactose [60].

Helicobacter pylori

Helicobacter pylori (synonym of *Campylobacter pylori*) is a microaerophilic bacterium implicated in a variety of human gastric diseases, including antral gastritis, peptic ulcer and gastric cancer [61]. Notably, *H. pylori* exhibits an unusual complexity in carbohydrate-binding specificity with interactions through sialylated oligosaccharides, gangliotetraosylceramide, Lewis b (Le^b) antigen, monohexosylceramide, lactosylceramide, lactotetraosylceramide, sulfatide and heparan sulfate, reflecting the complex interrelationship with its host.

Among other *H. pylori* adhesins, two have been shown to interact in a Sia-dependent manner. While the Sia-bind-

Table 2. Bacteria and their Sia-specific lectins.

Species	Lectin[1]	Specificity	3D structure [Ref.]	Ref.
Gram-negative				
Escherichia coli	SfaI, II¸ SFaS	Neu5Gcα2,3Gal; Neu5Acα2,8Neu5Ac		[48]
	K99 fimbriae	Neu5Gcα2,3Galβ1,4Glc		[52]
	F41 fimbriae	Sia		[53]
	CFA I; CS2	Sia		[59, 60]
Helicobacter pylori	SabA	Siaα2,3		[64]
	HP-NAP	Neu5Acα2,3Galβ1,4GlcNAcβ1,3Galβ1,4 GlcNAc		[63]
		Sia		[66]
Helicobacter hepaticus	HA-A	Sia?		[169]
Helicobacter bilis	HA-A	Sia?		[169]
Haemophilus influenzae	HifA	GM3,GM1, GM2, GDla, GD2, GD1b		[170]
	HMW1	Siaα2,3		[70]
	P2, P5	Sia		[68]
Actinobacillus actinomycetemcomitans		Sia		[171]
Pasteurella haemolytica	adhesin	Neu5Ac		[69]
Neisseria meningitidis	OpcA; Opa	Neu5Ac	[172]	[173]
Neisseria subflava	Sia-1	Neu5Acα2,3Galβ1,4Glc		[174]
Brucella abortus	HA-A	Sia		[175]
Brucella melitensis	HA-A	Sia		[175]
Pseudomonas aeruginosa		Sialyl-Le^x; Siaα2,6		[176, 177]
Bordetella bronchiseptica	SBHA	Neu5Ac		[178]
Bordetella avium	HA-A	GD1a, GT1b		[179]
Moraxella catarrhalis	fimbrial protein	GM2		[180]
Flavobacterium psychrophilum	HA-A	Sia		[181]
Treponema pallidum		Sia		[182]
Gram-positive				
Streptococcus gordonii	GspB	Siaα2,3 ≥ Siaα2,6		[76]
	Hsa	Neu5Acα2,3Gal		[75]
Streptococcus sanguis	SrpA	Sia		[77]
Streptococcus mutans	PAc	Siaα2,6		[183]
Streptococcus mitis	SABP	Neu5Acα2,3Galβ1,3GalNac		[184]
Streptococcus suis		Neu5Acα2,3Galβ1,4G1cNAcβl-3Gal		[185]
Streptococcus pneumoniae	CbpA	Sia		[186]
Streptococcus oralis		Sia		[187]
Ureaplasma urealyticum	HA-A	Sia		[188]
Mycoplasma				
Mycoplasma pneumoniae	HA-A	Neu5Acα2,3Galβ1,4GlcNAcβ1,3		[189]
Mycoplasma gallisepticum	HA-A	Sia		[190]
Toxins				
Vibrio cholerae	cholera toxin	GM1	[191]	[82]
Vibrio mimicus	haemolysin	GD1a, GT1b		[192]
Clostridium botulinum	neurotoxin A-F	1b series gangliosides	[193]	[194]
Clostridium tetani	tetanus toxin	GT1b, GQ1b	[195]	[196]
Clostridium perfringens	delta toxin	GM2		[197]
Escherichia coli	heat-labile enterotoxin	GM1	[198]	[196]
Bordetella pertussis	pertussis toxin	GD1a; Neu5Acα2,6Galβ1,4GlcNAc	[199]	[200]

[1] HA-A, haemagglutinin activity observed.

ing lectin SabA recognizes all terminal α2,3-linked Sia regardless of the underlying glycan structure, the neutrophil-activating protein, HPNAP, binds solely Neu5Acα2,3Galβ1,4GlcNAcβ1,3Galβ1,4GlcNAc structures [62, 63]. Although whole *H. pylori* bacterial cells are able to bind Neu5Acα2,3Galβ1,4GlcNAcβ1,3Galβ1,4GlcNAc β-terminated glycosphingolipids, knockout experiments have shown that recognition is mediated solely by the SabA adhesin [64, 65]. Recently, a third α2,3-Sia-recognizing protein was identified from *H. pylori* [66].

Given that only inflamed healthy stomach tissue expresses high levels of Sia [67], it would appear that interactions with Sia may be more important in longer-term survival and maintenance of a chronic state than in me-

diating primary recognition events. A prominent feature of *H. pylori*-induced gastritis is infiltration of neutrophils into the gastric epithelium, leading to phagocytosis and an oxidative burst with production of reactive oxygen metabolites, which may provide the nutritional source for the bacterium [65]. Thus, initial attachment of *H. pylori* may be achieved through binding to receptors present in the normal gastric epithelium (e.g. Le^b antigen and lactotetraosylceramide), whereas the Sia binding capacity of *H. pylori* mediates adhesion through lectins such as SabA to the epithelium in the already diseased stomach [64].

Pasteurellaceae

Members of Pasteurellaceae are small rods that colonize the mucosal surface of the respiratory and genital tracts. Different members of the Pasteurellaceae group, such as *Haemophilus influenzae*, *Actinobacillus actinomycetemcomitans* and *Pasteurella haemolytica* have been found to possess Sia-specific lectins [68, 69]. The HMW1 and HMW2 proteins from *H. influenzae* are high-molecular-weight adhesins that mediate binding to cultured epithelial cells. HMW1-mediated adherence studies revealed the involvement of a surface glycoprotein containing *N*-linked oligosaccharide chains with terminal α2,3-linked Sia [70]. HMW1 binding to oropharyngeal epithelial cells and human erythrocytes was also inhibited by the gangliosides GM1, GM2 and GDla [71]. However, because GM1, GM2 and GDla are not involved in HMW1 attachment, a distinct receptor for HMW1 with a complementary function in the process of colonization has been suggested [70]. In addition, proteins P5 and P2, the most abundant major outer membrane proteins of *H. influenzae,* appear capable of interacting with mucin via Sia-containing oligosaccharides. Although this property may not impart long-term advantage on *H. influenzae*, in a normal host with intact mucociliary function it may facilitate the establishment of infection in conditions associated with an abnormality in mucus clearance, such as chronic bronchitis and cystic fibrosis [68].

Gram-positive bacteria

Streptococcus

Streptococcus gordonii and other species of the viridans group, such as *S. sanguis* and *S. oralis*, comprise a prominent group of oral bacteria that occur primarily on the human tooth surface, and are well-known for their ability to colonize damaged heart valves, as well as being among the most frequently identified primary etiological agents of subacute bacterial endocarditis.

Studies on the adhesion of viridans group streptococci to saliva-treated hydroxyapatite provided early evidence for bacterial recognition of Sia-containing salivary receptors [72]. Two Sia-binding adhesins have now been identified in different *S. gordonii* strains, designated GspB and Hsa. Both are members of a family of wall-anchored, serine-rich repeat proteins that recognize α2,3-linked Sia [73, 74]. Hsa in particular binds to *O*-glycosylated mucin-type glycoproteins, including salivary mucin MG2 and leukosialin (the major surface glycoprotein of human polymorphonuclear leukocytes). Moreover, Hsa as well as GspB seems to be involved in the aggregation of human platelets by *S. gordonii* through binding to platelet glycoproteins Ibα and IIb, an interaction implicated in the pathogenesis of infective endocarditis [75, 76].

Recently, the *S. sanguis* glycoprotein homologue of Hsa/GspB was identified and named SrpA. Like its *S. gordonii* homologues, SrpA is involved in platelet aggregation, mediated by binding to GPIbα in a Sia-dependent manner [77]. Furthermore, recent studies, together with the completion of various genome projects, have revealed Hsa/GspB homologues in other Gram-positive species [78, 79].

Toxins

In addition to adhesins, some bacterial pathogens express soluble lectins, which are typically toxins. This toxicity results from their ability to catalytically modify macromolecules that are required for essential cellular functions such as vesicular trafficking, cytoskeletal assembly, signalling or protein synthesis. To reach their targets, these proteins bind specific surface receptors before endocytosis and translocation across the internal membrane can occur. These toxins classically bind to oligosaccharide receptors on host cell surfaces, and many of them show high specificity toward Sia, generally located on gangliosides [80]. Many belong to the AB_5 family of toxins with an A-subunit carrying the catalytic domain of the toxin, while the B-subunit is responsible for binding the holotoxin to a receptor on the surface of the target cell, an obligatory step for the uptake of the enzymatic A-subunit. One of the best examples of a Sia-binding soluble lectin belonging to the AB_5 family is cholera toxin, produced by *V. cholerae.* The B-subunit exhibits specific binding to ganglioside GM1, delivering the A-subunit to the cytosol. This results in the overactivation of an intracellular signalling pathway in gastrointestinal epithelial cells, causing severe diarrhoea [81]. Other notable examples of Sia-dependent toxins are those from *Clostridium botulinum* and *Clostridium tetani*, the causative agents of botulism and tetanus, respectively, which both recognize gangliosides [82].

Protozoa

As we have shown, Sia-specific lectins play a key role in mediating adherence of pathogenic microorganisms to

their respective hosts. The number of organisms belonging to the kingdom Protozoa recognized as medically significant is increasing, particularly in developing countries where, for instance, *Plasmodium* sp., the causative agent of malaria, is of particular concern. Even though at this stage only a few Sia-specific lectins expressed by protozoal pathogens have been reported, the number is increasing (see Table 3). Thus far protozoan Sia-specific lectins have been described in *Leishmania* sp., *Tritrichomonas* sp., *Babesia* sp. as well as *Trypanosoma* sp. and *Plasmodium* sp., with the latter being the most extensively studied.

Trypanosoma

Trypanosomes, such as *Trypanosoma cruzi*, the etiologic agent of Chagas disease, express a surface-bound protein, called trans-sialidase (TS), which enables the parasite to acquire Sia from mammalian host glycoconjugates. In *T. cruzi,* the TS family is encoded by approximately 140 genes [83], many of which code for an inactive enzyme. Initial studies showed that an enzymatically inactive recombinant TS, which was able to agglutinate desialylated erythrocytes, possessed β-Gal binding activity [84]. More recent studies have shown that the inactive TS can also act as a Sia-recognizing lectin capable of stimulating $CD4^+$ T cell activation *in vitro* and *in vivo*. The sialomucin CD43 was identified as a counter-receptor for TS on $CD4^+$ T cells and tests revealed that the inactive TS displays a similar specificity to that described for active TS (specific for α2,3 linked Sia) [85]. The same group also showed that inactive TS from *T. cruzi* binds Sia and β-Gal residues in a sequential order mechanism, suggesting that binding of the sialyl residue induces a conformational switch that then permits interaction with β-Gal [86]. To our knowledge this is the first report of a lectin recognizing two distinct ligands by a sequential order mechanism and may have implications for the design of TS inhibitors.

Plasmodium

Although there are many intra-erythrocytic parasites, erythrocyte invasion has been most widely studied in *Plasmodium* species. *Plasmodium* species are the causative agents of malaria, a disease that afflicts millions

Table 3. Protozoa and their Sia-specific lectins.

Species	Lectin[1]	Specificity/ligand	3D structure [Ref.]	Ref.
Trypanosomatidae				
Trypanosoma cruzi	inactive TS (Tyr342His)	CD43 (leukosialin on $CD4^+$ T cells) (Neu5Acα2,3 > Neu5Acα2,6 > sLe^x)	[201][2]	[85]
Leishmania donovani	HA-A	Sia		[202]
Leishmania infantum	HA-A	Sia		[202]
Leishmania tropica	HA-A	Sia		[202]
Leishmania aethiopica	HA-A	Sia		[202]
Leishmania major	HA-A	Sia		[202]
Leishmania mexicana	HA-A	Sia		[202]
Leishmania enrietti	HA-A	Sia		[202]
Leishmania amazonensis	HA-A	Sia		[202]
Trichomonadidae				
Tritrichomonas mobilensis	TML	Neu5Acα2,6 > Neu5Acα2,3 > Neu5Ac		[203]
Tritrichomonas foetus	TFL	Neu5Ac > Neu5Gc > Neu5Acα2,3/6		[204]
Tritrichomonas suis	HA-A	Sia		[205]
Plasmodiidae				
Plasmodium falciparum	EBA-175	Neu5Acα2,3Gal (glycophorin A) > Neu5Acα2,6Gal	[97]	[89]
	EBA-140, BAEBL, PfEBP2	Sia (glycophorin C)		[90]
	EBA-181, JESEBL	Sia		[92]
		Sia (glycophorin B)		[94]
		Sia (receptor E)		[94]
	RfRh1, NBP1	Sia (receptor Y)		[206]
Plasmodium knowlesi	β protein	Sia (rhesus erythrocytes)		[207]
Babesiidae				
Babesia divergens		Sia (glycophorin A and B)		[208]
Babesia bovis		Neu5Acα2,3/6		[209]
Babesia equi		Neu5Acα2,3		[210]
Babesia caballi		Neu5Acα2,3		[210]

[1] HA-A, haemagglutinin activity observed.
[2] Represents crystal structure of active TS.

worldwide, with *P. falciparum* responsible for the most severe form of human malaria. Parasite invasion is composed of an initial phase of random cell-cell contact, followed by reorientation and specific receptor-ligand interactions and subsequent entry into host erythrocytes [87]. Parasite proteins, which mediate interaction with erythrocyte receptors, whether Sia-dependent or -independent, belong to a family of erythrocyte-binding proteins (EBP). The erythrocyte-binding antigen-175 (EBA-175) [88, 89] and its paralogue, EBA-140 [90, 91] and EBA-181 [92], are EBP of *P. falciparum* that belong to the Duffy binding-like protein family and require Sia on host receptors for binding and invasion.

P. falciparum utilizes a number of receptors on the erythrocyte surface for merozoite invasion. The glycophorins (A, B and C), sialoglycoproteins present on the erythrocyte surface, serve as the major receptors for Sia-dependent invasion of erythrocytes [93]. Glycophorin A has been identified as the binding partner of EBA-175 [89], whereas EBA-140 binds glycophorin C. Glycophorin B and the so-called receptor E can also bind *P. falciparum* in a sialidase-sensitive manner; however, the parasitic lectin responsible for binding in both cases remains to be identified [94]. The Sia-containing receptor for EBA-181 remains unidentified; however, it has been shown that it differs from the EBA-175 and EBA-140 receptors [92]. These studies and others [95, 96], which specifically investigated EBA-175 binding to glycophorin A, show that the binding specificity of each parasitic binding protein is defined not only by the presence of Sia but also by the protein backbone.

The recently published crystal structure of the erythrocyte binding domain of EBA-175, RII, complexed with α2,3-sialyllactose was found to be dimeric, displaying two prominent channels that contain four of the six observed glycan binding sites. Each monomer consists of two Duffy binding-like domains (F1 and F2), with F2 more prominently lining the channels and making the majority of the glycan contacts. Based on this structure a model, where RII dimerizes upon binding to glycophorin A on the erythrocyte surface during the invasion process, has been proposed [97].

Fungi

Sia-specific lectins have been isolated and characterized from the fruiting bodies of various mushroom species (see Table 4 and references therein). And even though some of these lectins may in the future prove useful tools for the analysis of Sia-containing glycoconjugates, their natural function, in many cases, is not clearly understood. However, the identification and isolation of Sia-specific lectins from pathogenic fungi, particularly airborne species that cause severe infections in immunocompromised individuals, has raised the possibility that the initial stages of infection, particularly fungal spore (conidia) binding to the lung epithelial cells, may be mediated through Sia (Table 4).

Dermatophytes

The first human pathogenic fungal species thought to possess a Sia-specific lectin were *Chrysosporium keratinophilum* and *Anixiopsis stercoraria* (synonym of *Aphanoascus fulvescens*) [98], which cause skin infections and onychomycosis in humans. Later, Sia-specific binding of dermatophytes to erythrocytes was observed. Dermato-

Table 4. Fungi and their Sia-specific lectins.

Species	Lectin[1]	Specificity/ligand	3D structure [Ref.]	Ref.
Mushroom				
Hericium erinaceum	HEL	Neu5Gc > Neu5Ac		[211]
Polyporus squamosus	PSA	Neu5Acα2,6Galβ1,4Glc/GlcNAc		[212]
Psathyrella vetutina	PVL	Neu5Aca2,3Galb1,4GlcNAc[2]		[213]
Paecilomyes japonica	PJA	Neu5Ac		[214]
Agrocybe cylindracea	ACG	Neu5Acα2,3Galβ1,4Glc	[215]	[216]
Pathogenic fungi				
Chrysosporium keratinophilum	HA-A	Neu5Ac		[98]
Anixiopsis stercoraria	HA-A	Neu5Ac		[98]
Dermatophyte (13 species)	HA-A	Neu5Ac		[99]
Penicillium marneffei		Neu5Ac/laminin and fibronectin		[217]
Aspergillus fumigatus	HA-A	Neu5Aca2,6GalNAc ?/laminin, fibronectin, fibrinogen, collagen		[105, 108]
Histoplasma capsulatum		Neu5Ac/laminin?		[102]
Macrophomina phaseolina[3]	MPL	Neu5Acα2,3Galβ1,4GlcNAc		[218]

[1] HA-A, haemagglutinin activity observed.
[2] Also binds GlcNAc.
[3] Phytopathogenic fungus.

phyte is the common name for a group comprising *Microsporum*, *Trichophyton* and *Epidermophyton* that causes skin disease (dermatophytosis) in animals, including humans. Species from all three genera were able to haemagglutinate rabbit erythrocytes; however, the haemagglutinating activity was greatest in the zoophilic (parasitic on animals) and anthropophilic (parasitic on man) dermatophytes, in comparison to geophilic (soil inhabiting) [99]. This indicates that those species that are primarily parasitic may express more Sia-specific lectin than those that normally inhabit the soil. The significance of Sia-specific lectins for the biology and pathogenicity of dermatophytes is at this stage difficult to ascertain; however, we may be able to draw some conclusions based on the importance of Sia recognition in the pathogenicity of other fungal species.

Histoplasma capsulatum

Histoplasma capsulatum is the causative agent of histoplasmosis, a severe pulmonary infection that is most commonly found in tropical areas. Early studies showed that a 50-kDa cell wall protein from *H. capsulatum* yeast was able to bind laminin with high affinity, a process thought to be important in the initial stages of infection [100]. Later, a specific lectin-like interaction between *H. capsulatum* yeast and macrophage-membrane proteins was identified [101]. This lectin-like binding was initially thought to be specific for β-Gal residues; however, more recent studies have shown binding to human erythrocytes may be mediated through Sia [102]. Treatment of erythrocytes with sialidase confirmed the importance of Sia; however, details regarding observed differences in 'attachment specificity' are not provided [103].

Aspergillus fumigatus

In developed countries, *Aspergillus fumigatus* is now regarded as the most important airborne fungal human pathogen, causing aspergilloma, allergic bronchopulmonary aspergillosis and the usually fatal disease invasive aspergillosis in immunocompromised individuals [104]. In all cases infection begins with the inhalation of conidia, which adhere and germinate in the lung.

The involvement of Sia in fungal biology has been most extensively studied in *A. fumigatus*, with several groups having investigated the Sia-dependent adhesion of *A. fumigatus* conidia to purified extracellular matrix protein (ECM) proteins [105, 106]. The participation of Sia in conidia-ECM adhesion was first proposed following the observation that conidial binding to laminin, fibrinogen and fibronectin could be inhibited by Neu5Ac and sialyllactose [107]. This led the authors to hypothesize the presence of a specific lectin on the conidial wall that binds Sia expressed on ECM proteins, a proposition later substantiated with the purification of a Sia-specific lectin from *A. fumigatus* [108]. To our knowledge this is the only Sia-specific lectin from a human pathogenic fungal species to be purified, thus providing an opportunity for the identification of similar lectins from other species, as well as providing the first clues as to the role of Sia in fungal pathogenicity.

The ability of the purified *A. fumigatus* Sia-lectin to agglutinate erythrocytes was affected only by Neu5Ac and Sia-containing glycoproteins, including bovine mucin and fetuin, whereas Sia-containing colominic acid and human orosomucoid (α_1-acid glycoprotein) were unable to inhibit haemagglutination activity. The major oligosaccharides present on human α_1-acid glycoprotein are tri- and tetra-antennary *N*-glycans with terminal Neu5Acα2,3/6Galβ1,4GlcNAc structures [109]. On the other hand, bovine mucin and fetuin contain a significant number of *O*-glycans with GlcNAcβ1,3(Neu5Acα2,6)GalNAc-Ser/Thr [110] and Neu5Acα2,3Galβ1,3(Neu5Acα2,6)GalNAc-Ser/Thr [111] structures, respectively. Therefore, it appears that the Sia-specific lectin from *A. fumigatus* may recognize Neu5Acα2,6GalNAc structures preferentially over other Sia linkages.

Plants

Even though only a handful of Sia-specific lectins have been identified and isolated from plants (see Table 5 and references therein), their historical importance in investigating the expression and biology of Sia is unquestioned. The occurrence, specificity and application of Sia-specific plant lectins has been reviewed elsewhere [112]; therefore, we will concentrate on the possible significance and function of these lectins in plant biology.

A popular theory used to account for the presence of Sia-specific lectins in plants concerns their involvement in plant defence [113]. Some arguments in favour of this role include the fact that these lectins specifically bind Sia [114, 115], a carbohydrate that plants themselves do not express. This may provide plants with a means of recognizing and combating sialylated pathogens. Further, the digestive tracts of animals capable of feeding on plants are covered with highly sialylated mucins, providing numerous ligands for Sia-specific lectins. Presumably, it is this binding of Sia-specific lectins from elderberry (*Sambucus nigra*) bark and wheat germ agglutinin that initiates the severe toxicity symptoms observed upon ingestion of plant lectins in higher organisms. The consequence of this is that elderberry, for example, is virtually never attacked in the wild [113]. Moreover, Sia-specific plant lectins, like other plant lectins, are predominantly localized in regions of the plant that are most susceptible to attack, and thus require an adequate protection strategy. For instance, the lectin from elderberry and the leguminous plant *Maackia amurensis* are found in the bark and seed, respectively [114, 115]. Peumans and van Damme have

Table 5. Plants and their Sia-specific lectins.

Species	Lectin[1]	Specificity/ligand	3D structure [Ref.]	Ref.
Maackia amurensis	MAL	Neu5Acα2,3Galß1,4GlcNAc	[118]	[114]
Maackia amurensis	MAH	Neu5Acα2,3Galß1,3[Neu5Acα2,6]GalNAc	[118]	[219]
Sambucus nigra	SNA	Neu5Aca2,6Gal		[115]
Sambucus canadensis	SCA	Neu5Acα2,6Gal		[220]
Sambucus sieboldiana	SSA	Neu5Acα2,6Gal		[220]
Trichosanthes japonica	TJA	Neu5Acα2,6Galβ1,4GlcNAc		[221]
Viscum album	ML-I	Neu5Acα2,6Galβ1,4GlcNAc		[222]
Saraca indica	saracin	Neu5Acα2,6/3Galβ1,4GlcNAc		[223]
Artocarpus integrifolia	jacalin	Gal and Man > Neu5Ac	[224]	[224]
Triticum vulgaris	WGA	internal GlcNAc > Neu5Ac	[225]	[226]
Morus alba	MLL	Neu5Gc		[227]
Lactuca scariole	PLA	Sia		[228]

[1] HA-A, haemagglutinin activity observed.

suggested that this aspect of plant physiology has a direct influence on viability, arguing that 'a growing plant that is half eaten... may [still] survive and even produce viable offspring' [113].

All of the above hypotheses are based on the assertion that a family of plant lectins actually exists that specifically binds Sia. However, this view is not universally shared. The presence of Sia, is thought by some, to only provide an acidic group that enhances the interaction [116]. That is, the interaction with Sia-containing glycoconjugates is believed to be a purely coincidental one. Evidence supporting this assertion includes the observation that free Sia does not interact with 'putative' Sia-specific plant lectins, with Gal or lactose being the real binding partner [117]. The crystal structure of *M. amurensis* lectin complexed with sialoglycoconjugates shows that a Gal residue occupies the primary binding site [118]. A sulfate group at C3 of Gal instead of Sia was found to bind *M. amurensis* lectin, indicating that only a charged group is required rather than a complete Sia molecule [119]. However, this would mean that the presence of a Sia molecule, regardless of linkage, would elicit the same effect. This is clearly not the case (see Table 5). Finally, Sia-specific lectins appear not to be as widespread in plants as would be expected given their proposed importance in plant defence. In spite of these arguments it is nevertheless difficult to reconcile this view with the fact that these lectins show exquisite specificity for what in essence are the natural sialoglycoconjugates that they would encounter in nature. It is therefore reasonable to suggest that due to evolutionary pressure placed on these plants by sialylated pathogens and/or predators, they have developed extremely specific defence mechanisms.

Animals

Sia-specific lectins have a wide variety of functions in animals. Even though for many individual lectins a function is unknown, for the majority their principal role seems to relate to the proper function of the immune system. There are a variety of lectins reported to bind Sia with high specificity in different animal phyla. This strict specificity is of obvious importance, ensuring proper function and regulation of these lectins. However, animals must also cope with numerous pathogens that, as we have already discussed, bind to their hosts via Sia. Since many pathogens have evolved lectins that are highly specific for Sia type and linkage, their hosts have needed to counter with various modifications to avert pathogenic entry, all the while ensuring that the proper ligands for their endogenous lectins are preserved. This 'arms-race', a term used by Angata and Varki [2], between host and pathogen not only explains the unusual structural complexity of Sia, but also the rapid evolution of some Sia-recognizing lectins, as is the case for the CD33-related siglecs [120]. This section will summarize the numerous Sia-binding proteins identified from invertebrate and vertebrate animals, their function and significance in animal biology.

Invertebrates

Sia-specific lectins have been isolated and characterized from various invertebrates, including molluscs, arthropods, echinoderms and urochordates, with many species containing more than one such protein (see Table 6 and references therein). Even though some of these lectins have served as useful tools for the analysis of Sia-containing glycoconjugates, their natural function, in many cases, is unclear. In a similar way to that postulated in plants, it has been assumed that most of these lectins play some role in the defence mechanism against bacterial infections [121].

Invertebrates, without the benefit of an adaptive immune system, possess an immensely strong innate immune response to counteract the continuous challenge of infection. Innate immunity is mainly targeted toward antigens such as lipopolysaccharides commonly present on the

Table 6. Invertebrates and their Sia-specific lectins.

Species	Lectin[1]	Specificity	Ref.
MOLLUSCA			
Bivalvia			
Modiolus modiolus	HA-A	Neu5Ac	[229]
Crassostrea gigas	HA-A	Neu5Ac	[230]
Crassostrea virginica		Sia	[231]
Mytilus edulis		Neu5Ac	[232]
Anadara granosa	AFL	Neu5Gc	[233]
Gastropoda			
Cepaea hortensis	agglutinin I	Neu5,9Ac_2	[234]
Achatina fulica	achatinin H	Neu5,9Ac_2	[235]
Pila globosa	PAL	Neu5Gc	[236]
Limax flavus	LFA	Neu5Ac > Neu5Gc	[237]
ARTHROPODA			
Chelicerata			
Limulus polyphemus	limulin	Neu5Ac, Neu5Gc	[238]
Tachypleus tridentatus	tCRP-2; tCRP-3	Neu5Ac	[239]
Tachypleus gigas	HA-A	Sia	[240]
Carcinoscorpius rotundicauda	carcinoscorpin	Neu5Gc, Neu5Acα2,6GalNAc-ol	[241]
Centruroides sculpturatus	HA-A	Neu5Ac, Neu5Gc	[242]
Mastigoproctus giganteus		Neu5Ac	[243]
Androctonus australis	HA-A	Neu5Ac, Neu5Gc	[244]
Vaejovis spinigerus	HA-A	Sia	[245]
Heterometrus granulomanus	scorpin	Neu5Ac, Neu5Gc	[246]
Aphonopelma chalcodes	HA-A	Sia	[247]
Ixodes ricinus		Sia	[248]
Ornithodoros moubata	dorin M	Neu5Ac	[249]
Ornithodoros tartakovskyi		Sia	[250]
Ornithodoros tholozani		Sia	[250]
Crustacea			
Paratelphusa jacquemontii	HA-A	*O*-Ac-Neu5Ac	[251]
Cancer antennarius	HA-A	Neu5,9Ac_2, Neu4,5Ac_2	[252]
Scylla serrata	HA-A	Neu5Gc	[253]
Liocarcinus depurator	HA-A	*O*-Ac-Neu5Ac	[254]
Homarus americanus	lobster agglutinin I	Neu5Ac	[255]
Macrobrachium rosenbergii	HA-A	Neu5Ac	[256]
Penaeus monodon	monodin	Neu5Ac	[257]
Litopenaeus setiferus	LsL	Neu5Ac, *O*-Ac-Neu5Ac	[258]
Litopenaeus schmitti	PPL	Neu5Ac	[259]
Tracheata			
Allomyrina dichotoma	Allo A-II	Neu5Acα2,6Galβ1,4GlcNAc	[260]
ECHINODERMATA			
Echinoidea			
Hemicentrotus pulcherrimus	350-kDa sperm-binding protein	Neu5AcGlcCer, (Neu5Ac)$_2$GlcCer	[123]
Strongylocentrotus purpuratus	350-kDa sperm-binding protein	Neu5AcGlcCer, (Neu5Ac)$_2$GlcCer	[123]
UROCHORDATA			
Styela plicata		Neu5Ac	[261]
Halocynthia pyriformis		Neu5Ac, Neu5Gc	[261]

[1] HA-A, haemagglutinin activity observed; no structural information is currently available on any of the lectins listed here.

surface of potential pathogenic Gram-negative bacteria. Invertebrate lectins seem to participate in the innate immune response by inducing bacterial agglutination or activation of phagocytes through binding to Sia on foreign cells (opsonin activity) [121].

Furthermore, Sia-binding lectins can express direct haemolytic activity as shown for a Sia-specific lectin called limulin from the American horseshoe crab *Limulus polyphemus,* where the plasma-based cytolytic system seems to be mediated by this single protein. Haemolysis depends on the Sia-binding activity of limulin, since sialylated glycoconjugates, such as fetuin, as well as Neu5Ac and colominic acid inhibit haemolysis, and desialylation of the target cells renders them immune to cytolysis [122].

Table 7. Vertebrate lectins that recognize Sia.

Lectin (synonyms)	Specificity	Expression	3D structure [Ref.]	Ref.
Selectins				
E-Selectin (CD62E;ELAM-1)	sLe^x, sLe^a	Act-endo	[262]	[126, 3]
P-Selectin (CD62P; GMP-140; PADGEM)	sLe^x, sLe^a	Act-endo, Plat	[262]	[126, 3]
L-Selectin (CD62L; Mel 14 antigen)	6′-sulfo sLe^x	Leuco		[126, 3]
Siglecs				
Siglec-1 (sialoadhesin)	Neu5Acα2,3Gal > Neu5Acα2,6Gal > Neu5Acα2,8	Macro	[263]	[128, 120]
Siglec-2 (CD22)	Siaα2,6Gal	B		[128, 120]
Siglec-3 (CD33)	Siaα2,6Gal > Siaα2,3Gal	My-pro, Mono, Macro		[128, 120]
Siglec-4 (MAG)	Neu5Acα2,3Gal	Oligo, Schwann		[128, 120]
Siglec-5	Siaα2,6Gal, Siaα2,3Gal > Neu5Acα2,8	Mono, Neutro, B, Macro		[128, 120]
Siglec-6 (OB-BP1)	Siaα2,6GalNAc (sialylTn)	Plac, B		[128, 120]
Siglec-7 (AIRM-1)	Neu5Acα2,8 > > Siaα2,6Gal > Siaα2,3Gal	Mono, NK	[264]	[128, 120]
Siglec-8	Siaα2,3Gal > Siaα2,6Gal	Eosino, Baso, Mast		[128, 120]
Siglec-9	Siaα2,3Gal, Siaα2,6Gal	Mono, Neutro, NK, B	[264]	[128, 120]
Siglec-10	Siaα2,3Gal, Siaα2,6Gal	Mono, NK, Eosino, B		[128, 120]
Siglec-11	Neu5Acα2,8Neu5Ac	Macro		[128, 120]
Others				
Complement factor H	Sia	blood		[265]
Interleukin-1α	biantennary Neu5Acα2,3Galβ1,4GlcNac	blood		[266]
Interleukin-1β	Neu5Acα2,3Galβ1-Cer (GM4)	blood		[266]
Interleukin-2	GD1b	blood		[267]
Interleukin-4	Neu5Ac1,7lactone	blood		[266]
Interleukin-7	Siaα2,6GalNAc (sialylTn)	blood		[266]
CD83	Sia	dendritic cells		[268]
L1	Neu5Acα2,3	neurons, $CD4^+$ T cells, Mono, B		[268]
Sia-binding proteins	Sia	rat sperm		[269]
Sia-binding protein	Sia	hamster sperm		[270]
Laminin	Siaα2,3Galβ1,4GlcNAc	extracellular matrix		[271]
Sarcolectin	Neu5Ac, Neu5Gc	placenta		[272]
Calcyclin	Neu5Gc	bovine heart		[273]
Calreticulin	Neu5Gc, Neu5Ac	ovine placenta		[274]
cSBL	Sia	frog egg		[275]
Sia-binding proteins	Sia	rat uterus		[276]

Information is given for *Homo sapiens* unless otherwise stated. Act-endo, activated endothelium; B, B cells; Baso, basophils; Eosino, eosinophils; Leuco, leucocytes; Macro, macrophages; Mast, mast cells; Mono, monocytes; My-pro, myeloid progenitors; Neutro, neutrophils; NK, natural killer cells; Oligo, oligodendrocytes; Plac, placental trophoblasts; Plat, platelets; Schwann, Schwann cells.

In addition to their role in the immune system, invertebrate lectins have been reported to play an important role in sperm-egg binding, as shown for the species-specific Sia-binding protein [350-kDa sperm-binding protein (SBP)] found in sea urchins [123].

Vertebrates

In vertebrates a variety of Sia-dependent lectins are known to play an important role in cellular communication with many of them found in the immune system (see Table 7 for full listing). The first vertebrate Sia-binding protein reported was Complement Factor H, a soluble serum factor that is part of the alternative pathway of complement, one of the earliest response components of the innate immune system [124].

Another important group of vertebrate Sia-binding proteins are the selectins, a family of C-type lectins that recognize sialyl Lewis x (sLe^x) and sialyl Lewis a (sLe^a) [125]. Together with other cell adhesion molecules, selectins mediate the adhesion and extravasation of leukocytes from the vascular bed into the surrounding tissue [126]. Furthermore, P-selectin has also been shown to be involved in tumour metastasis [127].

Siglecs are the largest family of sialic acid-recognizing lectins identified thus far with 11 members identified

in the human genome. Each siglec has a distinct preference for specific Sia type and linkage (see Table 7). Apart from Siglec-4, all siglecs are expressed by cells of the immune system. However, the function/s of most members of the siglec family are only poorly understood, though their cell-type-specific expression suggests involvement in discrete cellular events. For further information we recommend that interested readers see recent comprehensive reviews from Varki and Angata [120] and Crocker [128].

Conclusions

The immense structural diversity and wide distribution of Sia suggest that sialobiology has only scratched the surface regarding the identification of Sia-specific lectins in nature. This is particularly the case in the microbial world, where it seems probable that a vast array of Sia-specific lectins with unique specificities and functions exist that may not only prove useful tools for studying the biology of Sia, but may even represent novel targets for drug discovery.

The biological roles of many of the Sia-specific lectins described still remain unknown; therefore, detailed investigations are necessary to further analyse the interaction of Sia-binding proteins with their counter-receptors, as well as to elucidate the resulting signals controlling their function. This will not only broaden our understanding of the role of Sia in biological systems but also its relevance in biomedical research. Of particular importance is the need for sialobiologists to better understand how Sia and Sia-specific lectins drive the constantly evolving 'arms-race' being waged between pathogenic microorganisms and their hosts.

In this review we have summarized the key features relating to the occurrence, specificity and function of the Sia-specific lectins currently known, specifically those identified and characterized from microorganisms and non-vertebrate eukaryotes. The challenge now for Sialobiologists is to not only continue identifying, but also analysing the function of novel Sia-specific lectins, thus adding to the growing list summarized herein.

Acknowledgements. F. L. gratefully acknowledges the Deutsche Forschungsgemeinschaft (DFG) for the award of a Research Fellowship. J. T. gratefully acknowledges the Australian Research Council (ARC) for the award of an Australian Postdoctoral Fellowship. The authors also wish to thank Prof. Mark von Itzstein and Dr. Milton J. Kiefel for helpful suggestions and critical review of the manuscript.

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