Siglec Interactions with Pathogens

78

Takashi Angata and Ajit Varki

Contents

Abstract

Sialic acids are abundant acidic sugars decorating the cell surfaces of vertebrates and their close relatives, but rarely found in other taxa – with the striking exception of certain bacterial commensals and pathogens of vertebrates. Siglecs are a family of sialic acid recognizing receptors in mammals that mediate a variety of functions in different biological processes. The CD33-related Siglecs (CD33rSiglecs) are prominent on immune cells and play a role in distinguishing self and non-self by recognizing sialoglycans as "self-associated molecular patterns." Some pathogenic microorganisms exploit this self-recognition system by molecular mimicry of ligands or by direct binding, thus averting detection and elimination by the innate immune system. A subset of CD33rSiglecs with cell-activating properties may have evolved to counter such exploitation by

T. Angata (✉)
Institute of Biological Chemistry, Academia Sinica, Taipei, Taiwan
e-mail: angata@gate.sinica.edu.tw

A. Varki
Department of Cellular and Molecular Medicine, University of California, San Diego, La Jolla, CA, USA

N. Taniguchi et al. (eds.), *Glycoscience: Biology and Medicine*,
DOI 10.1007/978-4-431-54841-6_211

pathogens. In keeping with this, some show extreme sequence identity in their binding domains with respective inhibitory counterparts. Human null polymorphisms have been described for some CD33rSiglecs, which may be explained by counteracting evolutionary selective forces imposed by different pathogens. Two CD33rSiglecs appear to have been inactivated in our ancestors, just prior to the origin of the human species. Environmental factors associated with civilization may have also played a role in shaping the genetics and functions of these receptors.

Keywords

Molecular mimicry • Pathogens • Polymorphisms • Self-associated molecular patterns • Sialic acids

Introduction: Sialoglycans as Self-Associated Molecular Patterns (SAMPs)

Sialic acids are a group of acidic sugars with 9-carbon backbones, primarily found on the outermost ends of glycans displayed on vertebrate cell surfaces (Angata and Varki 2002). The distribution of sialic acids is restricted to vertebrates and their close relatives (e.g., echinoderms), with some exceptions, as explained later. These properties (i.e., cell-surface display and limited species distribution) makes them good candidates to be used as one of the "signatures of self" or "self-associated molecular patterns (SAMPs)," as opposed to "pathogen-associated molecular patterns (PAMPs)," i.e., molecular cues in the self/non-self discrimination by the vertebrate immune system (Varki 2011). In fact, sialic acids have long been known to interact with factor H, sparing host cell surfaces from the attack of alternate pathway of complement while allowing activation of complement system and formation of complement pore complex on foreign objects (e.g., bacteria, fungi, parasites) which do not express sialic acids. Another major group of proteins that recognize glycans containing sialic acids are Siglecs, a family of closely related lectins belonging to the immunoglobulin superfamily (Crocker et al. 2007). Most Siglecs are expressed on cells of immune system and have an inhibitory signaling property (by recruiting tyrosine phosphatases) that is compatible with their role as negative regulator of immune system to prevent development of autoimmunity (Lajaunias et al. 2005).

However, this self-recognition system involving sialic acids and Siglecs is not flawless. Once bacteria acquire the capability to display sialic acids (or its molecular mimicry) on their surface, the system can be exploited. Although the metabolic cost of sialic acid biosynthesis is relatively high as compared with more common 6-carbon sugars (as it requires *N*-acetylhexosamine and pyruvate for its biosynthesis), such a strategy has been indeed adopted by some bacteria.

Bacterial Molecular Mimicry That Targets the Sialic Acid-SAMP Recognition System

Some pathogenic bacteria (most of which are a part of normal flora and only cause diseases in an opportunistic mode) express sialic acids by various mechanisms, including (1) de novo biosynthesis by convergent evolution (Lewis et al. 2009), (2) scavenging of sialic acid or CMP-sialic acid from the host, and (3) adsorption of sialylated glycoconjugates from the host. In addition, some bacteria have developed proteins that "mimic" sialic acids. These molecular mimicry mechanisms have been shown to provide a selective advantage. Some examples of bacteria-Siglec interaction are listed in Table 1.

Sialic acid-dependent engagement of Siglec-9 by group B streptococcus (GBS) type III has been shown to dampen neutrophil responses to the bacteria (Carlin et al. 2009b). Moreover, engagement of Siglec-5 by group B streptococcus (GBS) type Ia was also shown to dampen neutrophil response, but in this case the interaction is independent of sialic acid and is instead mediated by β-protein on GBS (Carlin et al. 2009a). These results clearly demonstrate that bacterial pathogens, even the closely related ones, have adopted different strategies to engage inhibitory Siglecs to their advantage. These selective forces may have driven the rapid evolution of Siglecs, as suggested from the comparative genomic and functional analyses of CD33-related Siglecs (CD33rSiglecs) in closely related primate species (Angata et al. 2004; Padler-Karavani et al. 2014). These findings are consistent with the hypothesis that the evolution of CD33rSiglecs has been driven by the "dual" constraints imposed on them. This involves the necessity to avoid exploitation by the pathogens that engage Siglecs while also keeping up with the changing landscape of host sialome (which is driven by a separate set of pathogens that utilize sialic acids for infection).

While these "passive" strategies to hide away from pathogens may be necessary and effective, other strategies, such as "active" detection of these pathogens and counterattack, are conceivable. One candidate is the non-inhibitory Siglec-1 (sialoadhesin), which is expressed on some macrophages and can carry out phagocytosis of sialylated pathogens (Jones et al. 2003). Would there be any other countermeasures that vertebrates have adopted to counter these pathogens?

Activating-Type Siglecs: Countermeasures Against Siglec-Exploiting Pathogens?

Activating-type Siglecs, or those interacting with adapter protein DAP12 (that has immunoreceptor tyrosine-based activating motif (ITAM) and in turn recruits tyrosine kinase Syk), have been discovered in the past decade. By analogy to the Ly49 family of receptors, it has been proposed that the activating-type Siglecs may have emerged to counteract pathogens that exploit inhibitory counterparts (Angata et al. 2006). In the case of humans, Siglec-14 and Siglec-16 appear to fit this description, as they show extreme sequence identity with Siglec-5 and Siglec-11, respectively, and also show at least partial overlap with their respective inhibitory counterpart in terms of expression

Table 1 Pathogens known to interact with Siglecs

Pathogen	Pathogen molecule involved	Human Siglec involved	Outcome	References
Bacteria				
Neisseria meningitidis	Sialic acids on LPS	Sialoadhesin/ Siglec-1	Enhanced binding and phagocytosis	(Jones et al. 2003)
		Siglec-5		
Campylobacter jejuni	Sialic acids on LPS	Sialoadhesin/ Siglec-1	Modulation of factors affecting helper T-cell differentiation	(Avril et al. 2006; Heikema et al. 2010; Bax et al. 2011)
		Siglec-7		
Group B *Streptococcus* type III	Sialic acids on LPS	Siglec-9	Attenuated immune responses	(Carlin et al. 2009b)
		Siglec-E (mouse)		(Chang et al. 2014)
Group B *Streptococcus* type Ia	β-protein (Sia-independent)	Siglec-5/14	Siglec-5: attenuated immune responses	(Carlin et al. 2009a; Ali et al. 2014)
			Siglec-14: enhanced immune responses	
		Siglec-13 (chimpanzee)	Siglec-13: attenuated immune responses	(Wang et al. 2012)
Pseudomonas aeruginosa	Sialic acids on glycoproteins, adsorbed from human body fluid	Siglec-9	Attenuated immune responses	(Khatua et al. 2012)
Non-typeable *Haemophilus influenzae*	Sialic acids on LOS + Sia-independent interaction	Siglec-5/14	Siglec-5: attenuated immune responses	(Angata et al. 2013)
			Siglec-14: enhanced immune responses	
Viruses				
Porcine reproductive and respiratory syndrome virus (PRRSV)	Sialic acids on GP5 envelope glycoprotein	Sialoadhesin/ Siglec-1 (pig)	Enhanced infection	(Delputte and Nauwynck 2004; Van Breedam et al. 2010)

(*continued*)

Table 1 (continued)

Pathogen	Pathogen molecule involved	Human Siglec involved	Outcome	References
Human immunodeficiency virus (HIV)	Sialic acids on gp120 envelope glycoprotein	Sialoadhesin/ Siglec-1	Enhanced infection	(Rempel et al. 2008; Zou et al. 2011)
Varicella zoster virus (VZV), herpes simplex virus (HSV)	Glycoprotein B (involvement of sialic acids is not reported)	Myelin-associated glycoprotein/ Siglec-4	Enhanced infection	(Suenaga et al. 2010)
Eukaryotes				
Trypanosoma cruzi	Sialic acids acquired from host glycoproteins by *trans*-sialidase	Siglec-E (mouse)	Attenuated immune responses	(Erdmann et al. 2009)
Candida albicans	Zymosan (?)	Siglec-7	Enhanced immune responses	(Varchetta et al. 2012)

This table is updated from: http://www.glycoforum.gr.jp/science/glycomicrobiology/GM09/GM09E.html

patterns. While Siglec-14 has been shown to enhance activation of myeloid cells (Yamanaka et al. 2009; Yasui et al. 2011; Ali et al. 2014), the activating function of Siglec-16 has not been formally demonstrated.

However, a protein that can recognize a "signature of self" and activate the immune system may be a double-edged sword, as it could elicit an autoimmune reaction. While here must be some mechanism to prevent or control the damage, it is still elusive. Theoretically, there are some possible mechanisms for these receptors to activate the cells only when they are engaged by pathogens, while avoiding triggering autoimmune responses, such as requirement for the "priming" signal from other PAMP sensors, requirement for a ligand with much higher density than those found in the host, and specialization to the pathogen molecule and concomitant loss of SAMP recognition ability (as suggested for some other receptor families). Yet still, under some circumstances, activating-type Siglecs may harm the host and thus its absence may be favored. Loss of activating-type Siglecs in humans may be explained by this double-bind situation.

Polymorphic Loss of Human Activating-Type Siglecs

Human *SIGLEC14* and *SIGLEC16* have polymorphisms that render these genes inactive in some humans. In the case of *SIGLEC14*, an allele was found in which *SIGLEC14* and *SIGLEC5* are fused, resulting in the loss of the segment encoding

Siglec-14 (also resulting in the generation of *SIGLEC14/5* fusion gene, which encodes a protein identical to Siglec-5 in terms of amino acid sequence). In the case of *SIGLEC16*, a 4-nucleotide deletion polymorphism in exon 2 (coding N-terminal immunoglobulin-like domain) results in premature termination. Both of these "null alleles" are found at high frequency in modern human population (Yamanaka et al. 2009; Cao et al. 2008).

Loss of human Siglec-14 has been associated with two distinct outcomes: attenuated protection against GBS infection (Ali et al. 2014) and protection against exacerbation of chronic obstructive pulmonary disease (COPD) (Angata et al. 2013). It is more straightforward to interpret the former phenotype, as it can be explained by the loss of auxiliary signaling from Siglec-14 that enhances the inflammatory response against the pathogen and its elimination. On the other hand, the latter phenotype is somewhat more complex, and it is interpreted that the acute inflammatory response caused by bacterial infection (non-typeable *Haemophilus influenzae* was used as a model pathogen) on top of the underlying chronic inflammation triggers excessive inflammation, which results in the exacerbation of the disease.

COPD is a tobacco-related disease of predominantly older population (>40 years old), which argues against its possible involvement as a selective force in human evolution. However, a situation similar to COPD caused by indoor fire use and bacterial infection associated with it may be found in pre-historic human societies as well and may be relevant to the polymorphic loss of Siglec-14. Alternatively, co-infection by influenza virus and *Haemophilus influenzae*, which is known to result in much higher mortality rate, may provide an explanation. Cross-species transmission of bird influenza virus to human is enhanced in the environment that contains wild fowl (a natural host of the virus), domestic bird (e.g., chicken or duck), pig, and human. Such an environment is found in agricultural settings in Asia, and this fact might explain the higher frequency of *SIGLEC14*-null allele in Asia. In any case, because both fire usage and agriculture are unique to humans, it would be worth testing if the null polymorphism of *SIGLEC14* and *SIGLEC16* is unique to human as compared with other primates.

Complete Loss of Human Activating-Type Siglecs

In addition to the polymorphic loss of activating-type Siglecs in humans described above, *SIGLEC13* is universally lost in humans, while it is maintained in other lineages of primates (Angata et al. 2004). *SIGLEC17* is also inactivated by a single nucleotide deletion in exon 2 (and by a single nucleotide substitution that mutates the arginine residue essential for sialic acid recognition) in humans (Wang et al. 2012). Both chimpanzee Siglec-13 and functionally "resurrected" human Siglec-17 recognize sialylated bacteria (*Escherichia coli* K1 and GBS), although the recognition does not involve sialic acids but protein(s) on these bacteria. These Siglecs interact with DAP12 and enhance tumor necrosis factor α (TNFα) response of myeloid cells to low-dose lipopolysaccharide. Surprisingly, engagement of Siglec-13 by *E. coli* K1 or GBS results in the suppression of TNFα production (Wang et al. 2012).

Thus, it may be too simplistic to assume that all DAP12-associated Siglecs act as activating receptors under all circumstances. Regardless, population genetics-based analysis implies that the losses of both *SIGLEC13* and *SIGLEC17* were under positive selection (Wang et al. 2012). In other words, the losses of these Siglecs were beneficial for humans. Is there any coherent explanation for the emergence and subsequent loss of activating-type Siglecs?

An inhibitory Siglec may be lost if the benefit of its loss (avoidance of pathogen exploitation) outweighs the drawback (possible development of autoimmunity). Alternatively, an activating-type Siglec may be born to counter the pathogen that exploits the inhibitory Siglec. However, once the threat of the original pathogen is gone, excessive reaction against another pathogen (or commensal) or host's own cells may become a selective disadvantage, and absence of such activating-type Siglec may be preferred. Loss of the activating-type Siglec may occur under such situation, leaving the inhibitory Siglec unaffected (i.e., the activating-type Siglec works as a sacrifice for the inhibitory Siglec; Fig. 1). Thus, it is possible that the utility of activating-type Siglec as a countermeasure against a particular pathogen may be inherently short-lived. It would be interesting to test if the typical evolutionary life span of activating Siglecs is shorter than that of inhibitory Siglecs by comparative genomics analysis. Further study is obviously needed.

Examples of Siglec Interaction with Non-bacterial Pathogens

Other classes of microorganisms also appear to exploit "sialic acids-Siglecs" system to their benefit. Examples of non-bacterial pathogens that interact with Siglecs are listed in Table 1. Several enveloped viruses have been reported to interact with Siglecs, with overall end results in favor of the viruses (enhanced infection). Glycan compositions of enveloped viruses naturally reflect that of the host cells and should contain some sialic acids. As long as the density of sialic acids is sufficiently high, any envelope virus has opportunity to interact with Siglec, which may enhance their infection, as many Siglecs are known to be endocytosed upon engagement.

The eukaryotic pathogen *Trypanosoma cruzi* (the parasite that causes Chagas disease) uses its trans-sialidase to transfer host sialic acid to its cell surface mucin-like glycoproteins. This modification may enhance its binding to Siglecs (Erdmann et al. 2009). Although the model used by the study is mouse Siglec-E and not immediately relevant to humans, its human functional equivalent Siglec-9 may be involved in the case of human disease.

Conclusions and Perspectives

As the reported examples of pathogen-Siglec interactions are still limited, the conclusions and patterns we can draw from the literature may be still sketchy and insufficient. Further study will reveal rules and exceptions regarding the mechanisms and consequences of pathogen-Siglec interactions and provide clues for

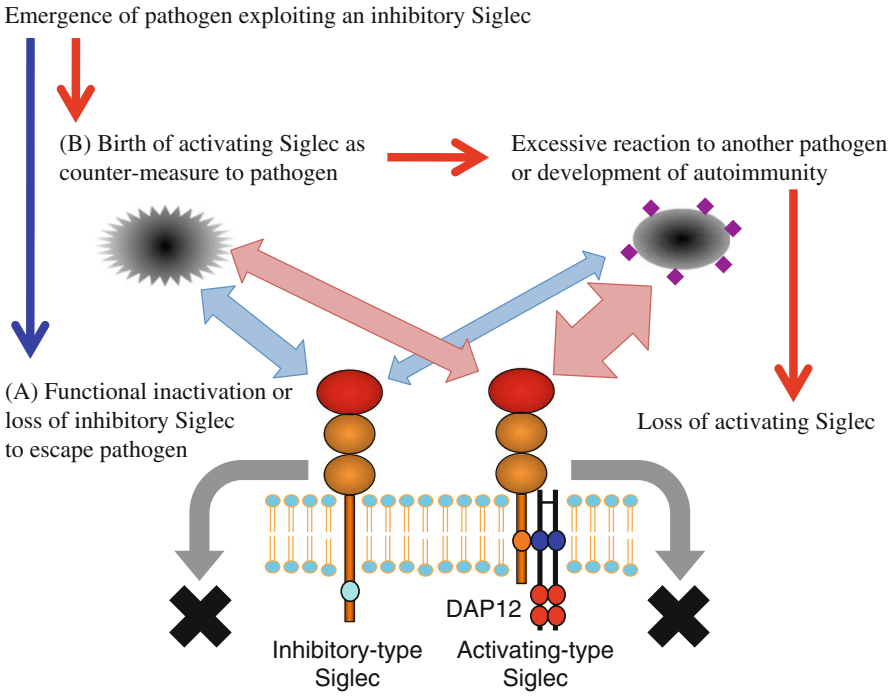

Fig. 1 Selective pressures by pathogens that may lead to "birth and death" of Siglecs. Inhibitory Siglecs are under selective pressure to evade pathogens, even while maintaining the function of recognizing the host sialome. Loss of an inhibitory Siglec may be positively selected (scenario A in the figure), in case the benefit of the loss (avoidance of pathogen exploitation) outweighs the drawback (possible development of autoimmunity). Alternatively, an activating-type Siglec may be born to counter the pathogen to alleviate the selective pressure applied by the pathogen (scenario B). However, excessive reaction against another pathogen/commensal or even host cells may develop, and absence of such activating-type Siglec may eventually become beneficial to the host under some circumstances (e.g., once the threat of the original pathogen is gone). Loss of the activating-type Siglec may be selected for under such condition. Genomic evidence suggests that such "birth and death" of Siglecs have been frequent events (Figure modified from Angata 2014)

prevention and treatment of infectious diseases. Meanwhile, recent studies have revealed that sialic acids are also involved in the regulation of interactions between gut microbiota and host gastrointestinal system (Ng et al. 2013). Further studies on the interplay involving sialic acids between bacterial flora and the host may reveal new and unexpected insights and are worth exploring.

References

Ali SR, Fong J, Carlin AF, Busch TD, Linden R, Angata T, Areschoug T, Parast M, Varki N, Murray J, Nizet V, Varki A (2014) Siglec-5 and Siglec-14 are polymorphic paired receptors that modulate neutrophil and amnion signaling responses to *Group B Streptococcus*. J Exp Med 211 (in press)

Angata T (2014) Roles of activating-type Siglecs on myeloid cell functions. J Phys Fit Sports Med 3 (in press)

Angata T, Varki A (2002) Chemical diversity in the sialic acids and related alpha-keto acids: an evolutionary perspective. Chem Rev 102:439–470

Angata T, Margulies EH, Green ED, Varki A (2004) Large-scale sequencing of the CD33-related Siglec gene cluster in five mammalian species reveals rapid evolution by multiple mechanisms. Proc Natl Acad Sci U S A 101:13251–13256

Angata T, Hayakawa T, Yamanaka M, Varki A, Nakamura M (2006) Discovery of Siglec-14, a novel sialic acid receptor undergoing concerted evolution with Siglec-5 in primates. FASEB J 20:1964–1973

Angata T, Ishii T, Motegi T, Oka R, Taylor RE, Soto PC, Chang YC, Secundino I, Gao CX, Ohtsubo K, Kitazume S, Nizet V, Varki A, Gemma A, Kida K, Taniguchi N (2013) Loss of Siglec-14 reduces the risk of chronic obstructive pulmonary disease exacerbation. Cell Mol Life Sci 70:3199–3210

Avril T, Wagner ER, Willison HJ, Crocker PR (2006) Sialic acid-binding immunoglobulin-like lectin 7 mediates selective recognition of sialylated glycans expressed on Campylobacter jejuni lipooligosaccharides. Infect Immun 74:4133–4141

Bax M, Kuijf ML, Heikema AP, van Rijs W, Bruijns SC, Garcia-Vallejo JJ, Crocker PR, Jacobs BC, van Vliet SJ, van Kooyk Y (2011) Campylobacter jejuni lipooligosaccharides modulate dendritic cell-mediated T cell polarization in a sialic acid linkage-dependent manner. Infect Immun 79:2681–2689

Cao H, Lakner U, de Bono B, Traherne JA, Trowsdale J, Barrow AD (2008) SIGLEC16 encodes a DAP12-associated receptor expressed in macrophages that evolved from its inhibitory counterpart SIGLEC11 and has functional and non-functional alleles in humans. Eur J Immunol 38:2303–2315

Carlin AF, Chang YC, Areschoug T, Lindahl G, Hurtado-Ziola N, King CC, Varki A, Nizet V (2009a) Group B streptococcus suppression of phagocyte functions by protein-mediated engagement of human Siglec-5. J Exp Med 206:1691–1699

Carlin AF, Uchiyama S, Chang YC, Lewis AL, Nizet V, Varki A (2009b) Molecular mimicry of host sialylated glycans allows a bacterial pathogen to engage neutrophil Siglec-9 and dampen the innate immune response. Blood 113:3333–3336

Chang YC, Olson J, Beasley FC, Tung C, Zhang J, Crocker PR, Varki A, Nizet V (2014) Group B streptococcus engages an inhibitory Siglec through sialic acid mimicry to blunt innate immune and inflammatory responses in vivo. PLoS Pathog 10:e1003846

Crocker PR, Paulson JC, Varki A (2007) Siglecs and their roles in the immune system. Nat Rev Immunol 7:255–266

Delputte PL, Nauwynck HJ (2004) Porcine arterivirus infection of alveolar macrophages is mediated by sialic acid on the virus. J Virol 78:8094–8101

Erdmann H, Steeg C, Koch-Nolte F, Fleischer B, Jacobs T (2009) Sialylated ligands on pathogenic *Trypanosoma cruzi* interact with Siglec-E (sialic acid-binding Ig-like lectin-E). Cell Microbiol 11:1600–1611

Heikema AP, Bergman MP, Richards H, Crocker PR, Gilbert M, Samsom JN, van Wamel WJ, Endtz HP, van Belkum A (2010) Characterization of the specific interaction between sialoadhesin and sialylated Campylobacter jejuni lipooligosaccharides. Infect Immun 78:3237–3246

Jones C, Virji M, Crocker PR (2003) Recognition of sialylated meningococcal lipopolysaccharide by siglecs expressed on myeloid cells leads to enhanced bacterial uptake. Mol Microbiol 49:1213–1225

Khatua B, Bhattacharya K, Mandal C (2012) Sialoglycoproteins adsorbed by *Pseudomonas aeruginosa* facilitate their survival by impeding neutrophil extracellular trap through siglec-9. J Leukoc Biol 91:641–655

Lajaunias F, Dayer JM, Chizzolini C (2005) Constitutive repressor activity of CD33 on human monocytes requires sialic acid recognition and phosphoinositide 3-kinase-mediated intracellular signaling. Eur J Immunol 35:243–251

Lewis AL, Desa N, Hansen EE, Knirel YA, Gordon JI, Gagneux P, Nizet V, Varki A (2009) Innovations in host and microbial sialic acid biosynthesis revealed by phylogenomic prediction of nonulosonic acid structure. Proc Natl Acad Sci U S A 106:13552–13557

Ng KM, Ferreyra JA, Higginbottom SK, Lynch JB, Kashyap PC, Gopinath S, Naidu N, Choudhury B, Weimer BC, Monack DM, Sonnenburg JL (2013) Microbiota-liberated host sugars facilitate post-antibiotic expansion of enteric pathogens. Nature 502:96–99

Padler-Karavani V, Hurtado-Ziola N, Chang YC, Sonnenburg JL, Ronaghy A, Yu H, Verhagen A, Nizet V, Chen X, Varki N, Varki A, Angata T (2014) Rapid evolution of binding specificities and expression patterns of inhibitory CD33-related Siglecs in primates. FASEB J 28:1280–1293

Rempel H, Calosing C, Sun B, Pulliam L (2008) Sialoadhesin expressed on IFN-induced monocytes binds HIV-1 and enhances infectivity. PLoS One 3:e1967

Suenaga T, Satoh T, Somboonthum P, Kawaguchi Y, Mori Y, Arase H (2010) Myelin-associated glycoprotein mediates membrane fusion and entry of neurotropic herpesviruses. Proc Natl Acad Sci U S A 107:866–871

Van Breedam W, Van Gorp H, Zhang JQ, Crocker PR, Delputte PL, Nauwynck HJ (2010) The M/GP(5) glycoprotein complex of porcine reproductive and respiratory syndrome virus binds the sialoadhesin receptor in a sialic acid-dependent manner. PLoS Pathog 6:e1000730

Varchetta S, Brunetta E, Roberto A, Mikulak J, Hudspeth KL, Mondelli MU, Mavilio D (2012) Engagement of siglec-7 receptor induces a pro-inflammatory response selectively in monocytes. PLoS One 7:e45821

Varki A (2011) Since there are PAMPs and DAMPs, there must be SAMPs? Glycan "self-associated molecular patterns" dampen innate immunity, but pathogens can mimic them. Glycobiology 21:1121–1124

Wang X, Mitra N, Secundino I, Banda K, Cruz P, Padler-Karavani V, Verhagen A, Reid C, Lari M, Rizzi E, Balsamo C, Corti G, De Bellis G, Longo L, Beggs W, Caramelli D, Tishkoff SA, Hayakawa T, Green ED, Mullikin JC, Nizet V, Bui J, Varki A (2012) Specific inactivation of two immunomodulatory SIGLEC genes during human evolution. Proc Natl Acad Sci U S A 109:9935–9940

Yamanaka M, Kato Y, Angata T, Narimatsu H (2009) Deletion polymorphism of SIGLEC14 and its functional implications. Glycobiology 19:841–846

Yasui K, Angata T, Matsuyama N, Furuta RA, Kimura T, Okazaki H, Tani Y, Nakano S, Narimatsu H, Hirayama F (2011) Detection of anti-Siglec-14 alloantibodies in blood components implicated in nonhaemolytic transfusion reactions. Br J Haematol 153(6):794–796

Zou Z, Chastain A, Moir S, Ford J, Trandem K, Martinelli E, Cicala C, Crocker P, Arthos J, Sun PD (2011) Siglecs facilitate HIV-1 infection of macrophages through adhesion with viral sialic acids. PLoS One 6:e24559