Chapter 8
Siglecs at the Host–Pathogen Interface

Yung-Chi Chang and Victor Nizet

Abstract Siglecs are sialic acid (Sia) recognizing immunoglobulin-like receptors expressed on the surface of all the major leukocyte lineages in mammals. Siglecs recognize ubiquitous Sia epitopes on various glycoconjugates in the cell glycocalyx and transduce signals to regulate immunological and inflammatory activities of these cells. The subset known as CD33-related Siglecs is principally inhibitory receptors that suppress leukocyte activation, and recent research has shown that a number of bacterial pathogens use Sia mimicry to engage these Siglecs as an immune evasion strategy. Conversely, Siglec-1 is a macrophage phagocytic receptor that engages GBS and other sialylated bacteria to promote effective phagocytosis and antigen presentation for the adaptive immune response, whereas certain viruses and parasites use Siglec-1 to gain entry to immune cells as a proximal step in the infectious process. Siglecs are positioned in crosstalk with other host innate immune sensing pathways to modulate the immune response to infection in complex ways. This chapter summarizes the current understanding of Siglecs at the host–pathogen interface, a field of study expanding in breadth and medical importance, and which provides potential targets for immune-based anti-infective strategies.

Keywords Sialic acid · Streptococcus · Pattern-recognition receptor · Trans-infection

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8.1 Introduction

Sialic acid-binding **i**mmuno**g**lobulin-type **lec**tin**s** (Siglecs) are cell surface receptors belonging to the immunoglobulin (Ig) superfamily. The extracellular domains of these receptors comprise one ligand-binding V-set domain and a variable number of C2-set domains, with high-sequence similarities to the variable and constant region of antibodies, respectively. Siglecs are mostly located on the cell surface of hematopoietic cells, with the exception of Siglec-4 (Schwann cells) and Siglec-6 (epithelial cells). Until now, 14 human Siglecs and 9 murine Siglecs have been identified with different preferences for binding to terminal sialic acids (Sia) on glycan structures in a linkage-sensitive fashion. The arginine residue in the Siglec V-set domain is critical for contacting the carboxyl group of the Sia to form a salt bridge that stabilizes the binding interaction.

Phylogenetically, Siglec family members can be subdivided into two groups: First, there are Siglecs that are conserved among different species, but showing low-sequence identity to one another, including Siglec-1, Siglec-2, Siglec-4, and Siglec-15. The other group comprises the so-called CD33 (Siglec-3)-related Siglecs (CD33rSiglecs), which show low gene conservation but possess higher degrees of sequence identity among the subfamily members. Both conserved Siglecs and CD33rSiglecs include activating and inhibitory receptors. The inhibitory Siglecs contain an immunoreceptor-based inhibition motif (ITIM) in their intracellular domain, conferring the ability to antagonize immune signaling pathways through the recruitment of the SHP phosphatases. Conversely, activating Siglecs have an aspartic acid residue in their trans-membrane domain that associates with immunoreceptor-based activation motif (ITAM)-containing adaptor DAP12 (DNAX-activation protein of 12 kDa) to promote signaling and immune responses. Lastly, Siglec-1 does not possess a functional intracellular domain and is not known to signal directly, but rather plays a role in cell–cell and cell–microbe interactions.

8.2 Siglecs in Bacterial Infection

Glycans are ubiquitous on eukaryotic cell surfaces via their incorporation in glycoproteins, glycosphingolipids, and glycerophosphatides. In mammalian cells, Sia is usually the outmost sugar residue on the oligosaccharide chains of cell surface or serum glycoconjugates, where it functions in recognition and anti-recognition phenomena ranging from the regulation of complement activation to the control of cell–cell apposition (Varki 1993). Like their host cells, bacteria have also evolved complex biosynthetic pathways to produce a diverse array of carbohydrates that form the building blocks of capsular polysaccharides (CPS), lipopolysaccharides (LPS), lipooligosaccharides (LOS), and peptidoglycans. These specialized bacterial glycans play pivotal roles in a number of biological processes, particularly mediating microbe–host interactions during the onset and development of infectious disease.

It has been long known that the bacterial CPS represents a key virulence factor for most encapsulated bacterial pathogens by protecting them from immune clearance within the host. Some bacterial capsules interfere with the binding and activation of complement factors on the bacterial surface by inhibiting the C3b convertase or recruiting inhibitory complement factor H (Cross and Kelly 1990). Bacterial capsules exerting this immune resistance mechanism usually contain sialic or polysialic acids or hyaluronic acid (HA), structurally identical or similar to the polysaccharides found in mammalian tissues, as exemplified by *Escherichia coli* K1, *Neisseria meningitidis* types B and C, or group A or group B *Streptococcus* (Stevens et al. 1978; Wessels et al. 1989; Foley and Wood 1959; Dale et al. 1996). Envelopment in these host-like capsular structures confers resistance to complement-mediated killing and phagocytic uptake by neutrophils and macrophages, increasing the chance of bacterial survival and dissemination into host tissues. In addition to these passive mechanisms of protection, an emerging hypothesis has been raised based upon the discovery of inhibitory members of the Siglec protein family on immune cells. Researchers have explored whether these host-mimicking pathogens can blunt activation of antimicrobial responses via engagement of inhibitory Siglecs using the Sia in their CPS. In parallel, studies have asked how hosts have evolved to better recognize and destroy such camouflaged pathogens. The interplay between a particular sialylated human pathogen, group B *Streptococcus* (GBS), and host immune responses serves as a good first example to illustrate the role of Siglecs and bacterial expression of Sia in the pathogenesis of infection.

GBS is a leading cause of neonatal pneumonia, sepsis, and meningitis and is increasingly recognized as a pathogen in elderly and immunocompromised adult populations (Heath and Schuchat 2007; Thigpen et al. 2011; Skoff et al. 2009). GBS can be classified into ten serotypes varying in structural and antigenic features, but which share in common the presence of a terminal Sia residue that closely resembles the one presented throughout the abundant surface glycocalyx of all human cells (Cieslewicz et al. 2005). Sialylated CPS from different GBS serotypes interacts with several human Siglecs in a Sia- and serotype-specific manner (Carlin et al. 2007). Through this Sia molecular mimicry, GBS engages inhibitory human Siglec-9 receptors on neutrophils, resulting in reduced production of reactive oxidative species (ROS) and neutrophil extracellular traps (NETs), which together impair bactericidal activity (Carlin et al. 2009b). Recently, GBS Sia engagement of Siglec-9 on human platelets to suppress their activation and release of antimicrobial peptides (AMPs) was shown to contribute to GBS resistance to platelet killing (Uchiyama et al. 2019). Corroborating these findings, transgenic mice expressing a soluble Siglec-9 receptor, which acts as a decoy to prevent neutrophil suppression, were more resistant to GBS infection in vivo (Saito et al. 2016). Linkages to the underlying sugar chain as well as the substitution at certain carbon positions of Sias are critical in determining their binding specificity for Siglecs. One study used isogenic mutants with different *O*-acetylation phenotypes to show that Sia *O*-acetylation protects GBS CPS from enzymatic removal by microbial sialidases produced by commensal microbes occupying in the same mucosal niche as GBS (Weiman et al. 2009). However, the same modification markedly reduced GBS binding to human Siglec-9, such that

highly *O*-acetylated GBS mutants were less able to accomplish Sia-mediated neutrophil suppression and showed reduced virulence in vivo (Weiman et al. 2009, 2010). These observations suggest that GBS must balance competing evolutionary selective pressures to fine tune the *O*-acetylation level of CPS Sias to maximize its survival advantage in the host.

The role of GBS CPS Sia engagement of inhibitory Siglecs in the context of in vivo infection was first addressed in Siglec-E deficient mice due to the similarity of function and cellular distribution between human Siglec-9 and murine Siglec-E. Upon lower dose GBS challenge intranasally or intravenously, Siglec-E deficient mice showed increased production of several inflammatory cytokines and had reduced dissemination of the pathogen to the brain (GBS meningitis). However, exaggerated inflammatory mediators and reduced anti-inflammatory cytokine IL-10 production were observed in the Siglec-E deficient mice during a high-dose lethal challenge with GBS (Chang et al. 2014a). Thus, the sum consequence of the GBS molecular mimicry and inhibitory Siglec engagement is likely to vary based upon the site, stage, and magnitude of infection. Importantly, in addition to Sia-dependent Siglec engagement, certain GBS strains can use the surface-anchored β protein to bind human Siglec-5, another inhibitory Siglec preferentially expressed on macrophages and neutrophils. This protein-mediated engagement increased bacterial attachment to the macrophage surface, but simultaneously paralyzed macrophage killing functions, leading to a net reduction of phagocytosis, ROS production, NET formation, and bactericidal activity (Carlin et al. 2009a).

To counteract inhibitory Siglec hijacking strategies of bacterial pathogens, host Siglec-1 (sialoadhesin, CD169) plays a crucial role in limiting bacterial dissemination. This receptor, uniquely expressed in the marginal metallophilic and subcapsular sinus macrophages, recognizing the same key Sia epitope on the GBS surface, however lacks an intracellular ITM motif (Crocker and Gordon 1989; Crocker et al. 1994). Siglec-1 binding to GBS CPS Sia promoted phagocytic and bactericidal activity of macrophages in vitro and restricts GBS dissemination in vivo (Chang et al. 2014b). Loss of Siglec-1 expression not only affected the macrophage sampling and trapping capabilities but also the production of anti-GBS antibodies, suggesting a key role in optimization of antigen presentation and subsequent adaptive immune response against sialylated pathogens (Chang et al. 2014b). Another evolutionary adaption of the host to defeat pathogen Siglec hijacking is the emergence of activating Siglecs with the potential to counteract inhibitory Siglec-mediated immune suppression. In 2006, Angata et al. discovered Siglec-14, which possesses nearly identical Sia-binding domain as inhibitory Siglec-5 through gene conversion, but is coupled with DAP12, an ITAM motif bearing adaptor (Angata et al. 2006). Thus Siglec-5 and -14 represent paired receptors with opposite signaling effects. For example, on neutrophils and amniotic epithelium, β protein-expressing GBS can bind to Siglec-5 and Siglec-14, with the latter engagement stimulating p38 MAP kinase and AKT signaling to promote more efficient bacterial clearance. Notably, a *SIGLEC14*-null polymorphism is present in some humans, caused by fusion between *SIGLEC14* and *SIGLEC5* genes, resulting in functional deletion of Siglec-14 expression (Yamanaka

et al. 2009). A genetic survey of the *SIGLEC14*-null polymorphism and GBS colonization and premature delivery found that *SIGLEC14*-null allele is associated with higher GBS colonization in mothers and more frequent premature birth of infants from GBS-positive pregnancies (Ali et al. 2014).

In addition to GBS, the pathogens *Escherichia coli* K1 and *Neisseria meningitidis* serotype B, important agents of bacterial meningitis in infants and children, possess sialylated capsules. The CPS produced by these two bacteria resembles the same poly-α2,8-Sia (PSA) structure abundantly expressed on neurons and the glia cells of the developing central nervous systems (CNS) is critical for neuron development and function (Finne 1982; Devi et al. 1991; Rutishauser 2008). The human-specific Siglec-11 shows a unique expression pattern in human microglia and selective binding preference to α2,8-linked Sias (Angata et al. 2002; Hayakawa et al. 2005). Engagement of Siglec-11 by endogenous host PSA exerts protective effects against inflammation-mediated neurotoxicity (Wang and Neumann 2010). The mimicry of mammalian PSA by *E. coli* K1 and *N. meningitidis* type B CPS may, therefore, target Siglec-11 expression on microglia to blunt immune responsiveness and facilitate neuroinvasion, consistent with the high rates of mortality and serious neurological sequelae seen with these pathogens (Robbins et al. 1974; Kaper et al. 2004). Interestingly, the activating Siglec-16, which shares over 99% of sequence identity to the first two Ig-like domain of Siglec-11 but is coupled with ITAM-containing DAP12, was later discovered to be a paired receptor of Siglec-11 allowing fine-tuning of immune responses (Cao et al. 2008). Pathogenic *E. coli* K1 engages inhibitory Siglec-11 through their PSA capsule to inhibit macrophage anti-bacterial functions. In contrast, activating Siglec-16 expressing macrophages recognizes the same epitope to promote elimination of pathogen (Schwarz et al. 2017). In sum, macrophage engagement of GBS β protein or *E. coli* K1 PSA capsule illustrates an evolutionary dynamic in which the activating member of the Siglec receptor pair may override the immune suppressive responses generated by pathogen mimicry of the inhibitory Siglec member.

In addition to the CPS, sialylation of LPS and LOS is also a prominent binding target of Siglecs. For example, Siglec-1 and Siglec-5 bind to the sialylated LPS of *N. meningitidis*, and cells expressing either Siglec internalized meningococci in a Siglec- and Sia-dependent manner (Jones et al. 2003). Strains of *Campylobacter jejuni* express various monosialylated and disialylated LOS with α2,3- or α2,3/2,8-linked Sia residues, respectively, which perfectly mimic host neural gangliosides GM1, GD1a, GD3, or GT1a. Colonization with *C. jejuni* strains possessing sialylated LOS is epidemiologically associated with higher risk of developing a postinfectious autoimmune neuropathy termed Guillain-Barré syndrome (Jacobs et al. 1996; Willison et al. 2016; Willison and Yuki 2002). Several human Siglecs recognize these particular sialylated LOS structures, although the functional consequences of this interaction require further investigation. Siglec-7, which is expressed on natural killer (NK) cells, monocytes, and dendritic cells (DCs), can mediate specific Sia-dependent interaction with *C. jejuni* LOS (Avril et al. 2006). *C. jejuni* strains recognized by Siglec-7 express terminal disialylated residues mimicking host GQ1b-like epitopes, including GD1c and GD3. The Siglec-7 binding signal of *C. jejuni*

correlates with its ability to elicit anti-GQ1b antibodies, and strains recognized by Siglec-7 were particularly associated with oculomotor weakness in Guillain-Barré syndrome and its so-called Miller-Fisher variant (Heikema et al. 2013). On the other hand, *C. jejuni* with α2,3-linked Sia on the LOS chain showed strong interaction with Siglec-1 (Heikema et al. 2010), which facilitated bacterial uptake and induce higher macrophage production of the pro-inflammatory cytokine IL-6 (Heikema et al. 2013). A key role of Siglec-1 in recognition of sialylated *C. jejuni* LOS was confirmed in Siglec-1 deficient animals. Bone-marrow-derived macrophages from mice lacking Siglec-1 showed greatly reduced phagocytosis of sialylated *C. jejuni*, coupled with reduced production of proinflammatory cytokines and type I interferon responses (Klaas and Crocker 2012).

Sialylated LOS is important in DC and macrophage activation as well as subsequent T cell polarization and B cell activation. Removal of Sia from the *C. jejuni* LOS causes reduced myeloid cell activation and subsequent B cell responses (Kuijf et al. 2010; Huizinga et al. 2012, 2013). Varied sialylated LOS structures differentially modulate DC-mediated T cell polarization in a Siglec-dependent manner, wherein the GD1a/GM1a mimic induced a more pronounced Th2 skewing, while the GD1c mimic preferentially stimulated Th1 responses (Bax et al. 2011). These observations suggest that targeting distinct DC-expressed Siglecs may represent a potential strategy for manipulating Th cell differentiation programs and forestalling autoimmune disease post *C. jejuni* infection. In addition to modulating host DC functions via its sialylated LOS, *C. jejuni* triggers IL-10 production of DCs via engaging Siglec-10 through the pseudaminic acid residues on its flagella (Stephenson et al. 2014). These abundant Sia and Sia-like *C. jejuni* surface structures (e.g. pseudaminic acid) help mediate a complicated interaction with host immune cells that may impact *C. jejuni* human disease associations, ranging from autoimmune neuropathies to asymptomatic colonization in individuals with repeated exposure to *Campylobacter* spp.

In addition to the well-studied microorganisms mentioned above, a growing list of bacterial species have been discovered to display sialoglycoconjugates on their surfaces, such as *Pseudomonas aeruginosa* (Khatua et al. 2010, 2012), *Klebsiella pneumoniae* (Lee et al. 2014), and nontypeable *Haemophilus influenzae* (NTHi) (Kalograiaki et al. 2016). *P. aeruginosa* recruits host sialoglycoproteins and displays them on the bacterial surface, and these absorbed Sias can enhance bacterial survival by reducing complement deposition and engaging inhibitory Siglec-9 to suppress neutrophil bactericidal machinery (Khatua et al. 2010, 2012). *K. pneumoniae* exhibiting a hypermucoviscosity phenotype possess abundant Sia CPS; blocking of the pathogen's ability to engage inhibitory Siglec-9 enhances neutrophil bactericidal activity (Lee et al. 2014). NTHi LOS also contains a terminal Sia residue that interacts with Siglec-14, which enhances inflammatory cytokine production in Siglec-14-expressing macrophages correlating to COPD exacerbation in human patients (Angata et al. 2013). All these observations suggest that Sia molecular mimicry by many medical important bacteria can interplay with various Siglecs to affect infectious risk and clinical disease manifestations.

Glycosaminoglycans (GAGs) are another family of complex carbohydrates ubiquitously present on mammalian host cell surfaces and in the extracellular matrix, regulating a wide range of biological functions from cell adhesion and cell migration to tissue repair and immune responses (Linhardt and Toida 2004). In another instance of molecular mimicry, GAG structures have been discovered in several gram-positive and gram-negative bacterial capsules (Wessels et al. 1994; Jann and Jann 1992; DeAngelis 2002). The GAG HA is structurally identical in animals and in the capsule of group A *Streptococcus* (GAS) where it is serving as a molecular camouflage to evade host immune responses (Wessels et al. 1994; Dale et al. 1996). Recently, GAS was shown to use its HA capsule to target Siglec-9 on neutrophils, thereby blocking NET formation and oxidative burst to inhibit bactericidal function (Secundino et al. 2016). It is an interesting example of convergent evolution that two structurally unrelated carbohydrates, Sia of GBS and HA of GAS, each target distinct epitopes in the V-set domain of inhibitory Siglec-9 to dampen immune responses and promote pathogen survival in the human host (Secundino et al. 2016).

8.3 Siglecs in Viral Infection

Although fundamentally distinct from the Sia molecular mimicry strategies employed by bacterial pathogens to engage inhibitory Siglecs for immune evasion, several lines of evidence indicate viruses can themselves take advantage of Sia-Siglec interactions for cell targeting, spreading, and trans-infection.

Human immunodeficiency virus-1 (HIV-1) exploits a Sia-Siglec axis to facilitate its entry into myeloid cells and *trans*-infection into $CD4^+$ T cells. Notably, Siglec-1 possesses a unique extended 17 Ig-like extracellular domain structure extending out from the surface glycocalyx in an un-masked state which makes it an ideal surface entry target. Moreover, in contrast to infected $CD4^+$ T cells, myeloid cells are relatively resistant to HIV-1-induced cytopathic effects and there is no obvious depletion of myeloid cells in HIV-1-infected patients. To escape from host immune surveillance, HIV-1 may have evolved to hijack this Siglec-1-mediated cellular recognition pathway for its own benefit, to hide within infected macrophages and *trans*-infect $CD4^+$ T cells for efficient viral spread.

In the manner of many enveloped retroviruses, the HIV-1 envelope glycoprotein gp120 is heavily glycosylated, and gp120 mutations that remove N-linked glycan sites on HIV (and simian immunodeficiency virus SIV) impair virus attachment and entry (Auwerx et al. 2008). A direct interaction of HIV-1 and Siglec was first reported by Rempel et al. in 2008, where expression levels of Siglec-1 were correlated to HIV-1 viral load, and Siglec-1 was proven to bind HIV-1 in a Sia-dependent manner and facilitate infection to a permissive reporter cell line (Rempel et al. 2008). Later gp120 was proven to serve as viral ligand for Siglec-1 and for several CD33rSigecs, including Siglec-3, -5, -7, and -9, with varying avidity and HIV-1 strain dependency. Moreover, this Siglec-gp120 interaction facilitates virus infectivity to macrophages and T cells (Zou et al. 2011; Varchetta et al. 2013). Mature DCs (mDCs) capture HIV-1 and

viral membrane gangliosides, then transfer the virus to bystander $CD4^+$ T cells via the established immunological synapses between these two immune cell types. Host cell-derived α2,3 sialylated glycosphingolipid (GSL) on the HIV-1 particle membrane is the ligand for Siglec-1 on mDC required for triggering mDC-mediated *trans*-infection of $CD4^+$ T cells in lymphoid organs (Yu et al. 2014; Izquierdo-Useros et al. 2012; Puryear et al. 2013). A population of cervical DCs at the lamina propria of the ectocervix and the endocervix that express Siglec-1 may be particularly important, and ex vivo studies suggest that $CD4^+$ T cell *trans*-infection from these cells can be blocked by addition of anti-Siglec-1 antibodies (Perez-Zsolt et al. 2019a).

A loss-of-function variant (Glu88Ter) of *SIGLEC1* gene was recently identified from the Exome Aggregation Consortium genetic database to be present in 1% of the human population. Monocytes isolated from individuals with this specific variant completely lack Siglec-1 expression and have reduced HIV capture and *trans*-infection phenotypes ex vivo. However, individuals carrying this truncated Siglec-1 protein do not show marked difference in HIV-1 acquisition and AIDS outcomes in vivo, which suggests an indispensable (and perhaps dominant) role of the classical HIV-1 infectious routes in the HIV-1 dissemination within the infected individuals (Martinez-Picado et al. 2016).

The importance of Siglec-1-mediated viral spreading has also been confirmed in vivo in murine retroviral infection models. Murine leukemia virus (MLV) is recognized by murine Siglec-1 through its sialylated gangliosides (Erikson et al. 2015; Sewald et al. 2015). MLV captured by Siglec-1-expressing sinus-lining macrophages and subsequent *trans*-infection into B-1 cells through their synaptic contacts was directly demonstrated by time-lapse intravital 2-photon laser scanning microscopy (Sewald et al. 2015). Virus capture and efficient MLV infection at the lymph node and spleen were significantly reduced by Siglec-1-targeting antibodies as well as in *Siglec1*$^{-/-}$ mice (Sewald et al. 2015). These data confirm a pivotal role of Siglec-1 in initial retroviral capture and suggest that Siglec-1 could represent a therapeutic target to reduce viral laden macrophage reservoirs and to prevent *trans*-infection. However, in a murine model of the splenomegaly-inducing retrovirus Friend virus complex (FVC) infection, Siglec-1-expressing macrophages capture of incoming blood-borne retroviruses limited their spread to erythroblasts in the red pulp where FVC manifests its pathogenesis (Uchil et al. 2019). In this case, Siglec-1-mediated FVC capture was beneficial, and further activated DCs and promoted cytotoxic $CD8^+$ T cell responses, promoting efficient clearing of FVC-infected cells (Uchil et al. 2019).

Another well-documented example of Siglec exploitation for viral entry and immune modulation is the example of porcine reproductive and respiratory syndrome virus (PRRSV). PRRSV infection is one of the most economically devastating diseases in the global pork industry. PRRSV has a narrow cell tropism, primarily targeting cells of the monocyte/macrophage lineage (Duan et al. 1997). Two cellular proteins, CD163 and Siglec-1 have been identified as the primary targets for PRRSV binding and internalization (Duan et al. 1998; Vanderheijden et al. 2003). α2-3 and, to a lesser extent, α2-6-linked Sias on the PRRSV virion mediate viral

attachment and infection alveolar macrophages, with Siglec-1 serving as the primary entry receptor responsible for Sia-dependent binding through its N-terminal V-set domain (Delputte and Nauwynck 2004; Delputte et al. 2007). Siglec-1 neutralization blocks PRRSV infection in a dose-dependent manner, and overexpression of Siglec-1 in non-permissive cells enhances PRRSV cell attachment and internalization (Duan et al. 1998; Vanderheijden et al. 2003). In subsequent studies, Sias on the viral envelope structural protein M/GP5 heterodimer were identified as the binding target of Siglec-1 (Van Breedam et al. 2010), and the interaction of PRRSV with Siglec-1 interferes with macrophage phagocytic activity, which may increase the incidence and severity of secondary bacterial infections complicating primary PRRSV disease (De Baere et al. 2012).

Since Siglec-1 and CD163 are the two key receptors for PRRSV entry and internalization into porcine alveolar macrophages, neutralization of these two viral receptors has been explored as a potential target to control PRRSV infection in pigs. Two recent reports support this therapeutic concept. Neutralization of PRRSV infectivity for porcine alveolar macrophages was achieved by addition of soluble Siglec-1 and CD163 Fc fusion proteins, or by recombinant adenovirus- or exosome-delivered microRNA that specifically targeted CD163 and Siglec-1 (Chen et al. 2014b; Zhu et al. 2014). In addition, pigs that received recombinant adenovirus-delivered soluble CD163 plus Siglec-1 had reduced PPRSV viral loads and fecal viral emission, concurrent with improved clinical scores and higher survival rates from the contagious infection (Xia et al. 2018). It is notable that an in vivo study conducted in *SIGLEC1* knockout pigs found that the absence of Siglec-1 expression does not alter to the clinical course and histopathology of PRRSV infection (Prather et al. 2013), implying a potential redundant function of CD163 and Siglec-1 in PRRSV infection and the importance of dual targeting for potential pharmacological interventions.

Although Siglec-1 and CD163 are general recognized as the key entry mediators for PRRSV infection, a recent report demonstrated that certain PRRSV strains can infect Siglec-1-deficient cells by exploiting Siglec-10 in the presence of CD163 (Frydas and Nauwynck 2016; Xie et al. 2017). Siglec-10 showed a higher affinity to type 2 PRRSV vs. type 1 PRRSV and mediates attachment and endocytosis of PRRSV in a Sia-dependent manner, while transfection of Siglec-10 into non-permissive cells also restored the PRRSV infectivity. These findings indicate that PRRSV can use several Siglecs to enter macrophages and may influence strain differences in pathogenesis (Xie et al. 2017). Of note, PRRSV lung infection induces minimal production of type I interferon and inflammatory cytokines compared to infections caused by swine influenza virus and porcine respiratory coronavirus (Van Reeth et al. 1999). Like other inhibitory Siglecs, porcine Siglec-10 contains one ITIM and one ITIM-like motif possibly, likely counteracting key immune activation pathways induced by viral infection (Crocker et al. 2007).

Budding from the GSL-enriched domain is a conserved feature of other enveloped viruses. Incorporation of host GSL into the viral envelope is found in Hendra and Nipah viruses, two enveloped RNA viruses of the family *Paramyxoviridae*, and these viruses can utilize the Sia-Siglec-1 axis to potentiate mDC-dependent capture and

trans-infection of T cells (Akiyama et al. 2014). Ebola viruses cause lethal hemorrhagic fever in humans, with many recent outbreaks on the African continent. Recently, Ebola virus entry into activated DCs was shown to involve Siglec-1 recognition of sialylated gangliosides anchored to Ebola virus membranes (Perez-Zsolt et al. 2019b). Blockade of Siglec-1 by specific monoclonal antibodies interrupted Ebola viral uptake and cytoplasmic entry, providing cross-protection against other GSL-containing viruses including HIV-1 (Perez-Zsolt et al. 2019b). This finding suggests that incorporation of GSLs in virus particle membranes facilitates Siglec-1 binding to mDC and may be a conserved mechanism for enveloped RNA viruses to exploit mDC for systemic virus dissemination.

Finally, Siglec-1 modulates T cell-mediated anti-viral responses during human respiratory syncytial virus (RSV) infection, with key differences between newborns and adults. Upon RSV infection, expression of Siglec-1 is upregulated on monocytes from both newborns and adults, whereas expression of Siglec-1 ligand, CD43, is only highly upregulated on adult $CD4^+$ T cells (van den Berg et al. 2001; Jans et al. 2018). This finding is consistent with observations that Siglec-1 inhibits IFN-γ production by adult $CD4^+$ T cells but not newborn $CD4^+$ T cells, although the detailed mechanism remains unknown (Jans et al. 2018).

8.4 Siglecs in Parasitic and Fungal Infections

Unlike many bacterial and viral infections, parasitic diseases caused by protozoa and helminths are often chronic, lasting months to years or even lifetimes. Animal parasites have developed remarkable strategies to interfere with or avoid immune clearance mechanisms to establish a chronic infection in their vertebrate hosts, including several examples of Sia-Siglec-mediated interactions that help achieve this immune evasion phenotype.

The protozoan parasite *Trypanosoma cruzi*, the causative agent of Chagas disease, illustrates well how Sia can be exploited by animal parasites to escape host immune surveillance, from the very first encounter with innate immune cells to the late-mounted adaptive immune responses. Although *T. cruzi* cannot synthesize Sias de novo, it uses its *trans*-sialidase (TcTS) enzyme to transfer Sias from host sialyl-glycoconjugates to its own surface mucins (Pereira 1983; Pereira et al. 1980). These highly sialylated mucin-like coats generated on the *T. cruzi* surface confer resistance to complement-mediated killing by impeding C3 convertase assembly, and block potential lytic effects of host anti-α-Gal antibodies that would recognize the otherwise exposed α-galactosyl epitopes on the mucin-like glycoproteins (Pereira-Chioccola et al. 2000; Tomlinson et al. 1994). Moreover, *T. cruzi* sialyl-glycoconjugates facilitate its binding to Siglec-1 on host macrophages, and this interaction may be involved in the initiation of trypomastigote infection (Monteiro et al. 2005). *T. cruzi* can also use its surface sialyl-glycoconjugates to engage Siglec-E on DCs and actively suppress their production of proinflammatory cytokine IL-12, impairing generation of protective Th1 responses (Erdmann et al. 2009).

Presence of α2-3 and α2-6 linked sialoglycans has also been discovered on another flagellated protozoa, *Leishmania donovani*, the causative organism of Indian visceral leishmaniasis (Chatterjee et al. 2003), such that high Sia-containing virulent strains bind both Siglec-1 and Siglec-5. The Sia-Siglec-1 interaction promotes macrophage uptake of the parasite promoting dissemination to other sites within the body, whereas the Sia-Siglec-5 binding suppresses ROS, NO, and Th2-dominant cytokine responses in infected macrophages by counteracting MAPK and PI3K/Akt signaling pathways (Roy and Mandal 2016).

Lastly, vaginitis caused by the fungal pathogen *Candida* is common and frequently recurrent condition in women's health. Recently, a combined global genetic and immune profiling study of clinical populations identified polymorphisms in *SIGLEC15* as candidate genetic predispositions involved in *Candida* vaginitis susceptibility (Jaeger et al. 2019). A particular SIGLEC15 polymorphism was associated with great inflammasome signaling and IL-1β production in response to *Candida* in vitro, and in vivo silencing of Siglec15 in a murine vaginitis model was associated with increased fungal burden and neutrophilic inflammation (Jaeger et al. 2019).

8.5 Crosstalk Between Siglec and Pattern-Recognition Receptors in Host Defense Mechanism

Recent evidence indicates that Siglecs functionally intersect with other host innate immune sensing pathways to modulate the response to viral and bacterial infection in important ways. For example, the RNA virus vesicular stomatitis virus (VSV) upregulates Siglec-G expression in macrophages through intracellular nucleic acid sensor RIG-I- or NF-κB-dependent mechanisms (Chen et al. 2013). Subsequent recruitment of SHP-2 phosphatase to the Siglec-G intracellular domain initiates a pathway for RIG-I degradation, thus suppressing anti-viral immunity. In corroboration, inactivation of Siglec-G protects mice against lethal VSV infection (Chen et al. 2013). VSV infection also results in upregulation of Siglec-1 in macrophages, which triggers a negative regulation pathway for TBK1 degradation via the ubiquitin ligase TRIM27, suppressing type I interferon production and allowing the virus to escape immune elimination (Zheng et al. 2015). Siglec-G expression is low in $CD8\alpha^+$ DCs, and Siglec-G deficient mice generate more antigen-specific cytotoxic T cell responses to inhibit intracellular bacterial infection (Ding et al. 2016).

One line of evidence developed in recent years suggests a potential for direct interactions between Siglec receptors, e.g. human Siglec-5 or -9 and murine Siglec-E and -F, and various toll-like receptors (TLRs) to downregulate the inflammatory pathways downstream of their pattern recognition (Chen et al. 2014a). Consequently, Siglec-E deletion was seen to boost DC responses to a broad range of microbial TLR ligands. In this model, activation of the mammalian sialidase Neu1 to the cell surface disrupts Siglec-E-TLR4 interaction, suggesting it can serve to derepress and allow positive feedback of TLR activation during infection (Chen et al. 2014a).

Caution is warranted, however, by another study applied quantitative proteomics to three different strains of Siglec-E-deficient mice. Quantitative proteomics found no consistent differences in TLR4 signaling or TLR4 endocytosis in response to LPS, nor did macrophages from the Siglec-E-deficient mice exhibit significant differences in uptake or killing of *Salmonella enterica* in vitro (Nagala et al. 2017).

8.6 Future Perspectives

Siglecs are important and broadly distributed lectin receptors of leukocytes uniquely poised to detect Sias and its perturbation during homeostasis and in disease states. The importance of Siglecs in immunopathology was proposed as early as the identification of Siglec-3 (CD33) and Siglec-2 (CD22) as biological markers of myeloid leukemias and B cell lymphomas, respectively. Mounting evidence supports the concept that Sia molecular mimicry serves as a virulence mechanism to subvert host innate immunity or to infect permissive target cells through an interplay with various Siglecs. As our understanding of Siglec influences on glycans-mediated host–pathogen interactions is now rapidly expanding and deepening, there is considerable interest in exploiting Siglecs for immunotherapy and disease prevention. Design of glycan-based therapeutics and their requirements for potency and specificity will likely provide a new biotechnological approach to effectively intervene in immunological processes to reduce the incidence and severity infectious diseases.

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