Siglecs and their roles in the immune system

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Abstract | Cell surfaces in the immune system are richly equipped with a complex mixture of glycans, which can be recognized by diverse glycan-binding proteins. The Siglecs are a family of sialic-acid-binding immunoglobulin-like lectins that are thought to promote cell–cell interactions and regulate the functions of cells in the innate and adaptive immune systems through glycan recognition. In this Review, we describe recent studies on signalling mechanisms and discuss the potential role of Siglecs in triggering endocytosis and in pathogen recognition. Finally, we discuss the postulated functions of the recently discovered CD33-related Siglecs and consider the factors that seem to be driving their rapid evolution.

V-set immunoglobulin domain
A protein domain that shows evolutionary similarity, in both linear sequence and folded structure, to the variable region domains of immunoglobulins. The domain folds into a sandwich of two β-pleated sheets consisting of antiparallel β-strands. V-set domains differ from immunoglobulin constant-region type 2 (C2)-set domains by having more β-strands in the β-pleated sheets.

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doi:10.1038/nri2056

The pioneering studies of Alan F. Williams and colleagues in the 1980s[1] laid the foundations for our current understanding of the roles of the immunoglobulin superfamily (IgSF) molecules as recognition molecules in the immune system. The immunoglobulin domain is a highly versatile fold that can be used to bind an almost infinite array of molecular structures, as illustrated by antibodies and T-cell receptors. The 'immunoglobulin-type' (I-type) lectins are a discrete subset of the IgSF that exploit the remarkable structural diversity of glycans in their recognition functions[2,3]. The Siglecs (sialic-acid-binding immunoglobulin-like lectins) are the best characterized I-type lectins[2–9]. They are type 1 membrane proteins displaying an amino-terminal V-set immunoglobulin domain that binds sialic acid and variable numbers (16 in the case of sialoadhesin) of C2-set immunoglobulin domains. They are categorized into two subsets on the basis of their sequence similarity and evolutionary conservation. Sialoadhesin (also known as Siglec-1 and CD169), CD22 (also known as Siglec-2), myelin-associated glycoprotein (MAG; also known as Siglec-4) and the recently discovered Siglec-15 (T. Angata, personal communication) are quite distantly related (~25–30% sequence identity) and have clear orthologues in all mammalian species examined. In comparison, the CD33-related Siglecs share ~50–99% identity but seem to be evolving rapidly by multiple processes, including gene duplication, exon shuffling, exon loss and gene conversion[10] (BOX 1). This has resulted in important differences in the repertoires of CD33-related Siglecs among mammalian species. Initial analyses of the genomes of fish, amphibians and birds indicate that, whereas typical CD33-related Siglecs are absent, a clear orthologue of MAG is present in all three taxa[11]. In humans, there are nine CD33-related Siglecs and one Siglec-like protein, whereas in mice there are five CD33-related Siglecs. So, it is difficult to assign orthologues, which has required the use of different numbering systems for the human and mouse CD33-related Siglecs (FIG. 1).

With the exception of MAG and Siglec-6, Siglec expression has been found mainly in the haematopoietic and immune systems (FIG. 1). Some are expressed in a highly cell-type-restricted pattern. For example, sialoadhesin is a macrophage-specific adhesion molecule and CD22 is a well-characterized B-cell inhibitory receptor that regulates multiple B-cell functions, including cellular activation thresholds and survival. In general, the CD33-related Siglecs show more complex expression patterns in the innate immune system in both humans and mice (FIG. 1). With the exception of resting T cells, most cell types in the human and mouse immune systems express at least one Siglec and others express several. Each Siglec has a unique specificity for sialylated ligands, making it more probable that each protein mediates a distinct, partially overlapping function. CD22 and most CD33-related Siglecs have one or more cytosolic immunoreceptor tyrosine-based inhibitory motifs (ITIMs). Classically, receptors with ITIMs function as inhibitory receptors and suppress activation signals that emanate from receptors associated with immunoreceptor tyrosine-based activation motifs (ITAMs) through the recruitment of tyrosine and inositol phosphatases[12]. By contrast, mouse CD33 and Siglec-H, and human Siglec-14 and Siglec-15 lack ITIMs. Two of these non-ITIM-containing Siglecs (Siglec-H and Siglec-14) have been shown to interact with DAP12 (also known as KARAP)[13,14],

Box 1 | Rapid evolution of CD33-related Siglecs

A striking feature of the CD33-related subfamily of sialic-acid-binding immunoglobulin-like lectins (Siglecs) is that they are evolving very rapidly. This involves almost every known form of genomic evolution, ranging from gene deletion, pseudogenization, gene-conversion events and exon shuffling, to specific amino-acid changes[9]. The last category is highly concentrated in the amino-terminal V-set domain, where sialic-acid recognition occurs[122]. We have proposed that this rapid evolution is a 'secondary Red Queen effect' mediated by the need of these binding domains to keep up with the rapidly evolving 'sialome' of the host (which may be driven by pathogens that bind sialic acids)[9]. An alternative, but not mutually exclusive, possibility is that pathogens expressing sialic acids are taking advantage of the CD33-related Siglecs, or vice versa. In this regard, the ancestral condition of at least some great ape Siglecs seems to be a preference for the non-human sialic acid *N*-glycolylneuraminic acid (Neu5Gc), which has never been reported to be synthesized by any pathogenic bacteria[26]. This indicates that the primary function of at least some CD33-related Siglecs is recognition of 'self'. Interestingly, the great majority of the reported *N*-acetylneuraminic acid (Neu5Ac)-expressing pathogens mainly infect humans[57]. So, it is possible that these pathogens actually emerged after human ancestors lost Neu5Gc expression and had to adjust their CD33-related Siglec binding specificity to accommodate Neu5Ac. It is also possible that some CD33-related Siglecs then evolved further to assist the human host in dealing with these Neu5Ac-expressing pathogens. In any event, the rapid evolution of such pathogens with their changing and diversifying sialylation may also be involved in driving the rapid evolution of CD33-related Siglecs. Interestingly, although there is some evidence for rapid evolution of CD33-related Siglecs in rodents, it is more obvious in primates and particularly striking in humans[122,123]. Further studies are required to see whether this rapid evolution in humans has resulted in polymorphisms associated with autoimmune disease susceptibility, as shown recently for other inhibitory receptors such as the low-affinity Fc receptor for IgG (FcγRIIb), immunoglobulin-like transcript 2 (ILT2), B- and T-lymphocyte attenuator 4 (BTLA4) and CD72 (REFS 124–127).

C2-set immunoglobulin domain
A protein domain that shows evolutionary similarity, in both linear sequence and folded structure, to the immunoglobulin constant region type 2 (C2) domains. The domain folds into a sandwich of two β-pleated sheets consisting of anti-parallel β-strands. C2-set immunoglobulin domains differ from domains of the variable region of immunoglobulins by having fewer β-strands in the β-pleated sheets.

Orthologue
Orthology describes genes in different species that derive from a common ancestor. Orthologous genes may or may not have the same function.

The Red Queen effect
A term that describes unremitting evolutionary arms races that can occur between competing species, or between a pathogen and its host. The term is derived from the Red Queen's comment in Lewis Carroll's *Through the Looking Glass*: "It takes all the running you can do, to keep in the same place."

an ITAM-containing adaptor that triggers both activating and inhibitory signalling[15]. Siglec-13, which is present in other primates but is specifically deleted in humans[9], also seems to recruit DAP12 (A.V., unpublished observations).

Taken together, it is clear that Siglecs in the immune system have the potential to mediate both cell–cell interactions and signalling functions. However, defining their precise functions and determining which ligands are biologically relevant pose an important challenge. This is beginning to be tackled using a combination of experimental approaches, including the production of genetically manipulated mice, biochemical analyses of ligand recognition and dissection of signalling pathways. In particular, several recent studies using mice that lack CD22, CD22 ligands or both, as well as mice expressing mutant forms of CD22 that cannot bind sialylated glycans, have begun to shed light on the complex factors involved. These have also provided a conceptual framework for understanding how the less well-characterized CD33-related Siglecs may contribute to regulation of leukocyte functions, as revealed in a recent study of Siglec-F-deficient mice[107]. Sialoadhesin (recognized by the antibody MOMA-1) is well known as a macrophage-specific marker and adhesion molecule but its biological functions have remained enigmatic. However, several recent studies of sialoadhesin-deficient mice have shown an unexpected role of this receptor in modulating immune and inflammatory responses. New data are available on the endocytic functions of Siglecs and their interactions with various sialylated pathogens that could be important in both host defence and pathogenicity. Finally, there is emerging evidence that CD33-related Siglecs have undergone significant changes during human evolution. In this Review, we discuss how these recent advances have significantly furthered our understanding of the roles of Siglecs in the immune system and wherever possible we attempt to relate these functions to glycan recognition and physiology.

Sialic-acid recognition by Siglecs

The mammalian glycome contains numerous sialylated glycans that can be potentially recognized as ligands by Siglecs (BOX 2). It is assumed that this recognition is important for modulating the functions of Siglecs as regulators of adhesion, cell signalling and endocytosis[5–9]. In general, Siglecs show low affinity (a K_d of 0.1–3 mM) for the sialic acid *N*-acetylneuraminic acid (Neu5Ac) α2–3 and α2–6 linkages to galactose (Neu5Acα2–3Gal and Neu5Acα2–6Gal) (FIG. 2) that are commonly found as terminal sequences on glycans of glycoproteins and glycolipids of most mammalian cells[16,17], and Siglecs have an overlapping specificity for such sialosides (sialic-acid-containing glycans). However, when examined for their ability to recognize a diverse set of natural sialoside structures found in mammalian species, each Siglec shows a characteristic specificity profile (FIG. 3). CD22 is unique in having a strong preference for Neu5Acα2–6Gal and Neu5Gcα2–6Gal structures[18,19]. Siglec-7 and Siglec-11 prefer sialosides with the Neu5Ac(α2–8)Neu5Ac structure[20,21].

Several Siglecs (such as Siglec-8 and Siglec-9) have differential specificity for sialosides that contain both sialic acid and sulphate, with the position of the sulphate being an important determinant of specificity[22–25]. In addition, Siglecs have different specificities for the many sialic acid species found in nature (FIG. 2). Of particular interest is the evolutionary loss of *N*-glycolylneuraminic acid (Neu5Gc) in humans, as Neu5Gc is the preferred ligand for at least some Siglecs in the closely related great apes[26].

The ligand-bound crystal structures of sialoadhesin and Siglec-7 offer insights into the structural basis for Siglec specificity[27–31]. In both cases, sialic acid is bound to a shallow pocket in the N-terminal immunoglobulin domain of the Siglec, with the negatively charged carboxyl group of sialic acid forming an important salt bridge with a conserved essential arginine (FIG. 2). As shown in domain-swapping experiments[20], the highly variable C–C′ loop (residues 70–75 in Siglec-7) of the V-set domain is a key determinant of Siglec specificity. In the crystal structure of Siglec-7 complexed with the Neu5Acα2–8Neu5Ac-containing ganglioside known as GT1b, the C–C′ loop undergoes a marked conformational change[30]. Although binding between natural sialosides and Siglecs is relatively weak, increased binding affinity has been seen for sialoadhesin, MAG and CD22 using sialic acid analogues that have aromatic substituents at the C-9 position of the monosaccharide[29]. These have been exploited for the creation of high-affinity ligand-based probes of Siglec function[29,31–35].

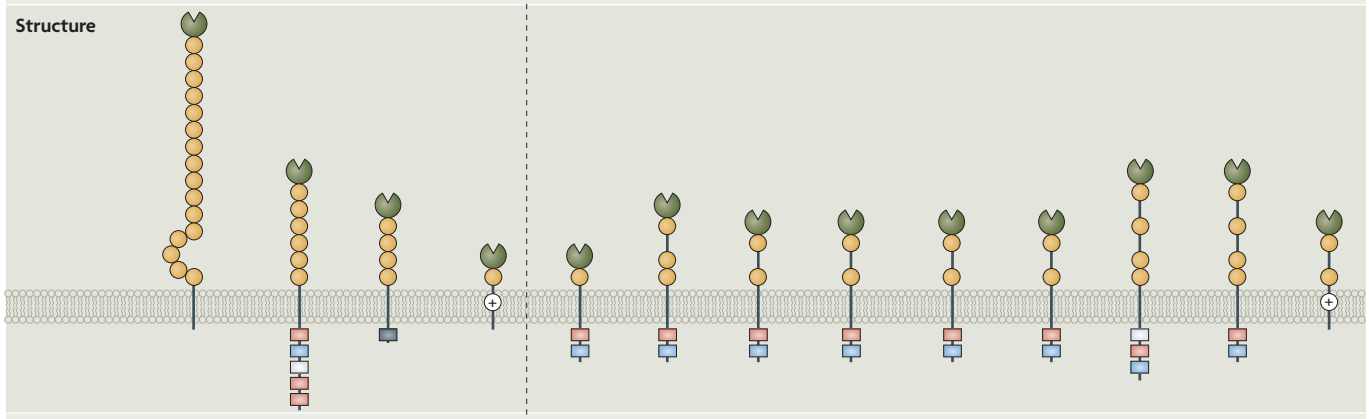
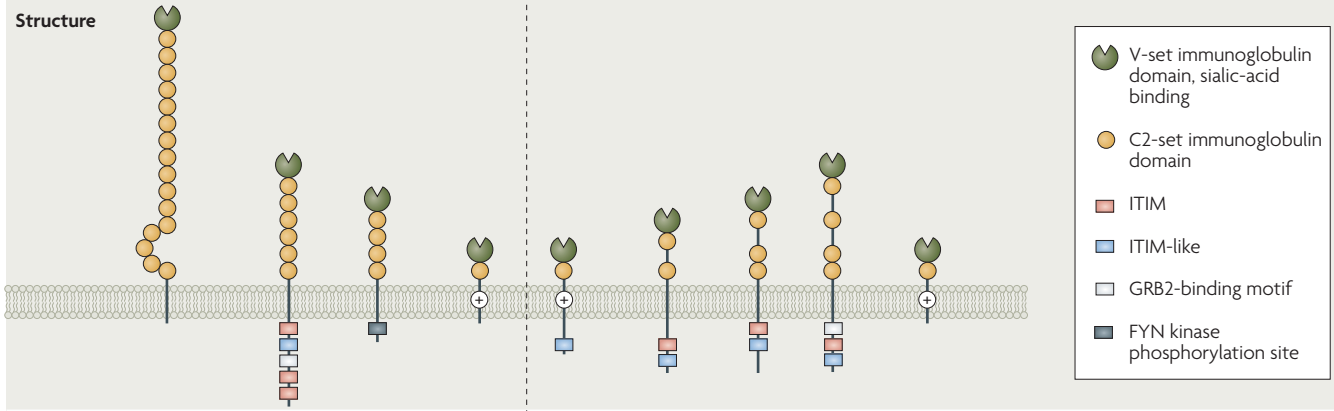
	Siglecs common to mammals				CD33-related Siglecs								
Human													
Structure													
Common name	Sialoadhesin	CD22	MAG	Siglec-15	CD33	Siglec-5	Siglec-6	Siglec-7	Siglec-8	Siglec-9	Siglec-10	Siglec-11	Siglec-14
Alternative name	Siglec-1, CD169	Siglec-2	Siglec-4	–	Siglec-3	CD170	CD327	CD328	–	CD329	–	–	–
Expression	Mac	B	OligoD, Schw	ND	MyP, Mo	N, Mo, (B)	Troph (B)	NK (Mo)	Eo (Ba)	Mo, N, cDC (NK)	B (Mo, Eo)	Mac	ND
Mouse													
Structure													
Common name	Sialoadhesin	CD22	MAG	Siglec-15	CD33	Siglec-E	Siglec-F	Siglec-G	Siglec-H				
Alternative name	Siglec-1, CD169	Siglec-2	Siglec-4	–	Siglec-3	–	–	–	–				
Expression	Mac	B	OligoD, Schw	ND	N	N, Mo, cDC	Eo	B	pDC (Mac)				

Figure 1 | **Siglec-family proteins in humans and rodents.** Sialic-acid-binding immunoglobulin-like lectins (Siglecs) are type 1 membrane proteins containing an amino-terminal V-set immunoglobulin domain that mediates sialic-acid recognition and varying numbers of C2-set immunoglobulin domains. Siglecs can be divided into two groups based on sequence similarity and evolutionary conservation. The CD33-related Siglecs differ in composition between species, share high sequence similarity in their extracellular regions and frequently contain conserved tyrosine-based signalling motifs in their intracellular domains. By contrast, there are orthologues, in all mammals examined, of sialoadhesin, CD22, myelin-associated glycoprotein (MAG) and Siglec-15 and they exhibit lower sequence similarity. Siglec-14 and Siglec-H have been shown to associate with DAP12 through a charged residue in their transmembrane domains. Electron microscopy has shown that purified sialoadhesin is a tadpole-shaped molecule of ~40 nm in which the carboxy-terminal immunoglobulin-like domains are arranged into a globular shape[128]. The cell-expression patterns are indicated on the basis of antibody labelling, except for Siglec-14 and Siglec-15, which have not yet been determined. The brackets indicate low levels of expression. Siglec-13 is present in baboons and chimpanzees and is specifically deleted in humans. Siglec-12 in humans has lost the ability to bind sialic acids and is, hence, designated as Siglec-XII (not shown). B, B cells; Ba, basophils; cDCs, conventional dendritic cells; Eo, eosinophils; GRB2, growth-factor-receptor-bound protein 2; ITIM, immunoreceptor tyrosine-based inhibitory motif; Mac, macrophages; Mo, monocytes; MyP, myeloid progenitors; N, neutrophils; ND, not determined; NK, natural killer cells; OligoD, oligodendrocytes; pDCs, plasmacytoid dendritic cells; Schw, Schwann cells; Troph, trophoblasts.

Box 2 | **Sialic acids as ligands for Siglecs**

Sialic acid refers to a family of sugars that are mostly derived from *N*-acetylneuraminic acid (Neu5Ac). Although there are more than 50 forms of naturally occurring sialic acid, mammals mainly express Neu5Ac, *N*-glycolylneuraminic acid (Neu5Gc) and 5,(7)9-*N*,*O*-diacetylneuraminic acid (Neu5,(7)9Ac_2). Humans lack Neu5Gc owing to a mutation in the *CMAH* (cytidine monophosphate-*N*-acetylneuraminic acid hydroxylase) gene, which encodes the enzyme required for the conversion of Neu5Ac to Neu5Gc[26]. Sialic acids are usually located at the exposed, non-reducing ends of oligosaccharide chains, and are transferred using α2–3, α2–6 or α2–8 linkages to subterminal sugars by a family of about 20 sialyltransferases. Siglec (sialic-acid-binding immunoglobulin-like lectin) binding to sialylated glycans can be greatly influenced by the type of sialic acid, its linkage to the subterminal sugar, the structure of the underlying glycan and other modifications such as sulphation. When sialylated oligosaccharide ligands are attached to protein and lipid carriers, the resulting glycoproteins and glycolipids have the potential to function as 'counter-receptors' for Siglecs and other glycan-binding proteins[47].

Immunoreceptor tyrosine-based inhibitory motif
(ITIM). A short peptide motif containing a tyrosine residue that is found in the cytoplasmic regions of many inhibitory receptors. The consensus sequence is (Ile/Val/Leu/Ser)-X-Tyr-X-X-(Leu/Val), with X denoting any amino acid. Following tyrosine phosphorylation by SRC-family protein tyrosine kinases, this provides a high-affinity docking site for the recruitment of cytoplasmic phosphatases and other signalling molecules with an appropriate SRC homology 2 (SH2) domain.

Immunoreceptor tyrosine-based activation motif
(ITAM). A short peptide motif containing tyrosine residues that is found in the cytoplasmic tails of several signalling molecules and in adaptors such as DAP12. The consensus sequence is (Asp/Glu)-X-X-Tyr-X-X-(Leu/Ile)-$X_{6–8}$-Tyr-X-X-(Leu/Ile), with X denoting any amino acid. It is tyrosine phosphorylated after engagement of the ligand-binding subunits, which triggers a cascade of intracellular events that usually results in cellular activation.

Glycome
The entire set of glycans in a cell, tissue or organism, under specified conditions. The sizes of glycomes are currently unknown but are likely to be many-fold larger than the size of the corresponding proteome owing to the combinatorial complexity and dynamic variability of glycan structures.

Cis *and* trans *ligands.* The local concentration of sialic acids on surfaces of immune cells is very high; for example, on B cells it has been estimated to exceed 100 mM[36]. As a consequence of this, and the fact that Siglecs usually recognize sialoside sequences that are commonly found on mammalian cells, Siglec binding sites are typically 'masked' by *cis* interactions with other glycan ligands expressed on the same cell[37–40]. This indicates that interactions with *cis* ligands may dominate over interactions with *trans* ligands in modulating the biological activities of Siglecs[7,9] (FIG. 4). One exception to this rule is sialoadhesin, which owing to its extended structure is thought to project its sialic-acid-binding site away from the plasma membrane, which reduces its *cis* interactions[41]. Despite the likely importance of *cis*-ligand interactions in Siglec function, they do not necessarily prevent the binding of ligands in *trans*. CD22 on B cells can redistribute to the site of contact with another cell expressing CD22 ligands[36]. Moreover, high-affinity synthetic sialoside probes can out-compete *cis* ligands for binding to CD22 on native B cells[34]. These results show that *cis* ligands downregulate, but do not preclude, binding of ligands in *trans*, and that equilibrium-based binding of Siglecs to *trans* ligands can occur dynamically in the presence of *cis* ligands. The biological significance of CD22 *trans*-interactions was explored by Lanoue *et al.* who showed that B-cell activation in response to antigen-presenting cells is suppressed if antigen and the CD22 ligand are expressed on the same cell[42]. This could be important for preventing autoantibody production by self-reactive B cells.

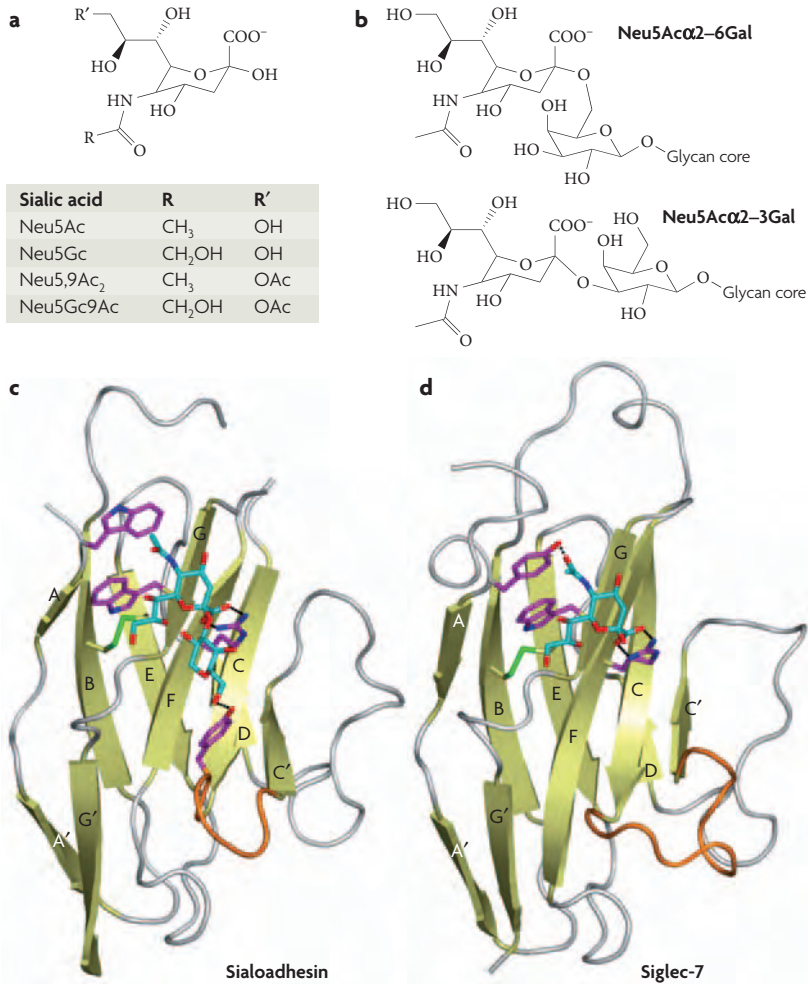
Siglec-7 is a natural killer (NK)-cell inhibitory receptor[43,44], which is masked by *cis* ligands that may include the preferred Neu5Acα2–8Neu5Ac-containing glycan[45]. In NK-cell cytotoxicity experiments with target cells engineered to overexpress this glycan structure, a small Siglec-7-dependent reduction in NK-cell cytotoxicity was observed and this was increased when NK cells were pre-treated with sialidase, which cleaves the *cis*-interacting ligands from the cell surface[46]. Such *trans*-interactions could contribute to the suppression of NK-cell cytotoxicity in tissues, such as the nervous system, in which the Neu5Acα2–8Neu5Ac-containing glycans are abundantly expressed.

In common with many glycan-binding proteins, high-avidity interactions of Siglecs require clustering of both receptors and ligands. For membrane receptors, clustering can be achieved by lateral diffusion in the plasma membrane or by the formation of multimeric complexes. For the glycan ligands, clustering can occur by presentation on suitable carriers, either protein or lipid, and/or by clustering on another cell surface. The resulting 'counter-receptors' have the potential to be recognized by glycan-binding proteins with high avidity and selectivity[47]. Although information on the nature of physiologically important ligands and counter-receptors of the Siglec family remains fragmentary, some insights have been obtained for CD22. B cells from mice deficient in the sialyltransferase ST6GAL1, which transfers sialic acids to galactose in α2–6 linkages to produce the preferred ligands for CD22, were devoid of *cis* ligands, which indicates that this sequence is required for binding by CD22 (REF. 48). A CD22–immunoglobulin Fc fusion protein has been shown to bind to CD45, serum IgM and many other B-cell (and T-cell) glycoproteins *in vitro*, and this implicates CD45 and IgM as candidate *cis* glycoprotein counter-receptors for CD22 on B cells[49–51]. However, using B cells that are metabolically labelled with a sialic-acid analogue containing a photo-activatable crosslinker, Han *et al.* found that CD45 and IgM are not preferentially recognized as *cis* ligands on the surface of the intact cell[33]. Instead, CD22 interacted preferentially in *cis* with glycans of neighbouring CD22 molecules. This is consistent with earlier crosslinking experiments[52,53], which also showed the formation of homomultimeric CD22 complexes involving protein–protein interactions. The basis for this selectivity may stem from the preferential concentration of CD22 in clathrin domains[35,54,55]. These studies underscore the potential difficulty in establishing the *in situ* ligands of Siglecs in their native context.

Pathogen ligands and innate immunity. Over 20 pathogenic microorganisms are known to have evolved the capacity to synthesize or capture sialic acids from their hosts and incorporate these into their own glycoconjugates. Examples include well-known bacterial pathogens, such as *Neisseria meningitidis*, *Haemophilus influenzae*, group B *Streptococcus*, *Campylobacter jejuni*, and several strains of *Escherichia coli* that cause infant meningitis, septicaemia, respiratory infections, diarrhoea and various other conditions[56]. Sialylation of glycoconjugates in these pathogens seems to be crucial for their survival in the mammalian host, possibly serving as molecular mimics of host cell surfaces to avoid immune attack[57]. It is also widely assumed that negatively charged sialic acids could serve to reduce pathogen interactions with the host by electrostatic repulsion, and/or by inhibiting the alternative pathway of complement activation. So far, comparatively little attention has been paid to the possibility that pathogen sialic acids are important for actually promoting infection or mediating an innate immune response by attachment to Siglecs. One clear example of this is porcine reproductive and respiratory syndrome virus (PRRSV), which is a sialylated enveloped virus that infects pig alveolar macrophages in a sialic-acid

Counter-receptor
A term used to describe the combination of oligosaccharide ligands coupled to protein or lipid carriers[47]. For many glycan-binding proteins, the affinity for oligosaccharide ligands is low, but high-avidity multivalent binding can occur when the ligands are appropriately displayed on carriers.

and sialoadhesin-dependent manner[58,59]. Sialoadhesin and several CD33-related Siglecs can interact with sialic acids on *N. meningitidis*, *C. jejuni*, group B *Streptococcus* and *Trypanosoma cruzi*[60–63] (TABLE 1). Siglec-dependent uptake of these pathogens could potentially benefit the host by promoting pathogen destruction and antigen presentation. It has also been suggested, but not proved, that sialylated pathogens modulate leukocyte activation through ITIM-mediated signalling of CD33-related Siglecs, thereby benefiting the pathogen by dampening inflammatory and immune responses[8,60,62,63].



Sialic acid	R	R′
Neu5Ac	CH_3	OH
Neu5Gc	CH_2OH	OH
Neu5,9Ac_2	CH_3	OAc
Neu5Gc9Ac	CH_2OH	OAc

Figure 2 | **Sialic acids and their interactions with Siglecs. a** | Sialic acid in mammals is commonly modified at the R and R′ positions with the substituents indicated. There are many other kinds of sialic acids in vertebrates, but apart from the commonly found forms shown here, Siglec (sialic-acid-binding immunoglobulin-like lectin) interactions with these have not been studied systematically. **b** | Two common sialoside sequences recognized as low-affinity ligands by many Siglecs are shown. **c** | Structure of the V-set domain of sialoadhesin (gold and grey) complexed with Neu5Acα2–3Gal (shown with turquoise carbons). Side chains of amino acids that make direct contact with the bound ligand are shown with purple carbons. The C–C′ loop that is implicated in fine specificity of Siglec binding is shown in orange. **d** | Structure of the V-set domain of Siglec-7 (gold and grey) complexed with Neu5Ac (shown with turquoise carbons). Side chains of amino acids that make direct contact with the bound ligand are shown with purple carbons. The C–C′ loop that is implicated in fine specificity of Siglec binding is shown in orange. Gal, galactose; Neu5Ac, *N*-acetylneuraminic acid; Neu5Gc, *N*-glycolylneuraminic acid. Images in parts **c** and **d** are reproduced with permission from REF. 28 © (2003) American Society for Biochemistry and Molecular Biology.

Sialoadhesin as a modulator of immune responses

Sialoadhesin was discovered as a sialic-acid-dependent macrophage adhesion molecule[64]. It is one of the largest members of the IgSF with an extracellular region made up of 17 immunoglobulin domains[65], a feature that is well conserved in mammals. Unlike most Siglecs, sialoadhesin lacks tyrosine-based signalling motifs and its cytoplasmic tail is poorly conserved, which suggests a primary role as a binding partner in cell–cell interactions, rather than in cell signalling.

There is increasing evidence to support a contribution for sialoadhesin in the pro-inflammatory functions of macrophages. Sialoadhesin is constitutively expressed on subpopulations of tissue-resident macrophages[66,67], and is rapidly upregulated by inflammatory macrophages. In proliferative glomerulonephritis, the expression of sialoadhesin correlates with proteinuria[68,69], and in individuals infected with HIV and that carry high viral loads, the sialoadhesin gene is induced up to tenfold in circulating monocytes[70]. It was recently shown that under normal conditions, sialoadhesin-deficient mice show only subtle alterations in the haematopoietic and immune systems, but in a model of peptide-induced experimental autoimmune uveoretinitis, the deficient mice showed reduced retinal inflammation, and T cells isolated from draining lymph nodes showed lowered proliferative responses *in vitro*[71]. Furthermore, in two genetically determined models of peripheral and central nervous system demyelination, disease in sialoadhesin-deficient mice was ameliorated and numbers of infiltrating $CD8^+$ T cells and macrophages at the sites of inflammation were reduced[72,73]. These new findings are consistent with a potentially important role of sialoadhesin in modulating T-cell function and activation during immune responses. An additional possibility is that sialoadhesin functions as a phagocytic receptor to clear sialylated pathogens.

Although the cellular and molecular bases for these effects require further investigation, sialoadhesin can mediate both sialic-acid-dependent and sialic-acid-independent interactions with cells of the immune system. Sialic-acid-dependent sialoadhesin interactions might be mediated by mucin-like molecules presenting high densities of sialylated *O*-linked glycans. For example, the sialomucins CD43 and mucin-1 were previously identified as putative T-cell and breast-cancer cell counter-receptors for sialoadhesin, respectively[74,75]. Sialic-acid-independent sialoadhesin interactions could involve the mannose receptor and macrophage galactose-type *N*-acetylgalactosamine-specific lectin 1 (MGL1). Both of these membrane lectins are expressed on dendritic cells (DCs) and have been shown to bind sialoadhesin extracted from lymphoid tissues[76,77]. Although DCs themselves do not normally express sialoadhesin, it can be induced on human monocyte-derived DCs following exposure to rhinoviruses *in vitro*[78]. Interestingly, these DCs were poor stimulators of T cells in mixed lymphocyte reactions, a feature that was partly attributed to the expression of sialoadhesin[78]. It is possible that when sialoadhesin is expressed by macrophages it is immunostimulatory, whereas on DCs it is immunosuppressive.

	Human					Mouse		
	CD22	Siglec-7	Siglec-8	Siglec-9	Siglec-10	CD22	Siglec-E	Siglec-F
α3 β4	0	+	+	+	+	0	++	++
α6 β4	+++	+	+	+	++	+	++	+/–
α6 β4	+++	+	+	+	+++	+++	+	0
α8 α3 β4	0	+++	+	0	0	0	++	0
6S α3 β4 α3	ND	++	+++	0	0	0	++	+++
6S α3 β4 α3	ND	+	0	+++	0	0	+	0

Neu5Ac Galactose GlcNAc Neu5Gc Fucose S Sulphate

Figure 3 | **Relative affinities of Siglecs with selected sialoside sequences.** A comparison of the sialoside specificities, obtained from glycan array analysis and competitive binding experiments, for several sialic-acid-binding immunoglobulin-like lectins (Siglecs) against selected sialoside sequences found in mammalian glycoproteins and glycolipids[17,22–24] (see also the Functional Glycomics web site). Despite the general low affinity of Siglecs towards the common mammalian sialoside structures containing the *N*-acetylneuraminic acid (Neu5Ac) α2–6 and α2–3 linkages, examination of the binding of each individual Siglec to a range of common sialoside structures shows that there is a unique sialoside specificity profile that is characteristic to each Siglec. +++, strong binding; ++, moderate binding; +, low binding; +/–, detectable binding; 0, no detectable binding; GlcNAc, *N*-acetylglucosamine; ND, not determined; Neu5Gc, *N*-glycolylneuraminic acid.

Clathrin domains
Specialized membrane microdomains that mediate endocytosis to early endosomes by a mechanism involving the formation of clathrin cages on the cytoplasmic face of the plasma membrane.

Proliferative glomerulonephritis
A group of inflammatory diseases affecting the glomerular apparatus of the kidney. These diseases have varied aetiologies but characteristically exhibit proliferation of mesangial cells and endocapillaries, and infiltration of leukocytes, such as macrophages and T cells.

Experimental autoimmune uveoretinitis
A photoreceptor-specific autoimmune disease that is inducible in several susceptible animal models with various retinal autoantigens. It resembles some human posterior uveoretinitis syndromes, including sympathetic ophthalmia, Vogt–Koyanagi–Harada disease, sarcoidosis, Behçet's disease and birdshot retinochoroidopathy.

Mixed lymphocyte reactions
A tissue-culture technique that is used for the *in vitro* testing of the proliferative response of T cells from one individual to lymphocytes from another individual.

LYN-deficient mouse model of lupus
A deficiency of the phosphokinase LYN results in a hyperimmune status leading to an autoimmune condition that is similar to the human disease systemic lupus.

Role of CD22 and its ligands

CD22 is a well-documented regulator of B-cell signalling, homeostasis and survival[7–9,79]. This Siglec is best known for helping to set a threshold for antigen-induced activation of B cells[80], an activity that involves as many as six tyrosine-based motifs in the cytoplasmic domain of CD22, including three ITIMs. B-cell receptor (BCR) ligation leads to increased phosphorylation of the ITIMs of CD22 by the SRC-family kinase LYN, which results in the recruitment of SHP1 (SRC homology 2 (SH2)-domain-containing protein tyrosine phosphatase 1) and the downregulation of BCR signalling[8,79]. However, this oversimplifies the complexity of CD22 signalling, as it can also recruit positive effectors of cell activation, including GRB2 (growth-factor-receptor-bound protein 2), SHC (SH2-domain-containing transforming protein C), PI3K (phosphoinositide 3-kinase) and PLCγ2 (phospholipase Cγ2)[79]. This results in activation of alternative signalling pathways that contribute to the regulation of B-cell activation. The impact of CD22 on these pathways probably depends on the manner of B-cell activation. Ligation of the BCR with either antigen or IgM-specific antibody, or simultaneous ligation of the BCR and CD40 (with IgM-specific and CD40-specific antibodies) result in the differential phosphorylation of CD22 tyrosine-based motifs both quantitatively and qualitatively[81,82]. Furthermore, CD22 does not seem to affect B-cell signalling when activated by ligation of cell-surface IgG[83]. A detailed molecular understanding of the role of CD22 will continue to evolve as B-cell signalling pathways become better defined[8,79].

Recent work on CD22 has provided important insights into how sialic-acid recognition can modulate its signalling functions. B cells of CD22-deficient mice exhibit hyperimmune responses *in vitro* and *in vivo*[8,79], consistent with the loss of negative regulation by ITIMs of CD22. Several CD22 functions, including BCR-dependent proliferation and B-cell turnover rates, depend on the ligand-binding function of CD22, as shown using mice that carry knock-in mutations of CD22 that ablate its ability to bind sialic acid[84]. In contrast to CD22-deficient mice, ST6GAL1-deficient mice (which lack CD22 ligands)[35,55,85] exhibit hypoimmune responses. B cells from mice that are deficient in both CD22 and ST6GAL1 behave similarly to those from CD22-deficient mice, which indicates that the immunodeficiency of ST6GAL1-deficient mice depends on the presence of CD22 (REFS 35,55,85). Following BCR ligation *in vitro*, the immunodeficiency caused by the absence of *cis* ligands in ST6GAL1-deficient mice is manifest by reduced B-cell proliferation and calcium flux, and increased CD22 phosphorylation and recruitment of SHP1 (REFS 35,55). Grewal *et al.* recently showed that ablating *St6gal1* in the LYN-deficient mouse model of lupus abrogated autoimmune responses[55], which indicates the therapeutic implications of inducing a CD22-ligand deficiency.

Insights into how the absence of CD22 *cis* ligands reduces B-cell signalling have been obtained by assessing the microdomain localization of CD22 in the membrane, relative to that of the BCR[35,55] (FIG. 5). In resting B cells,

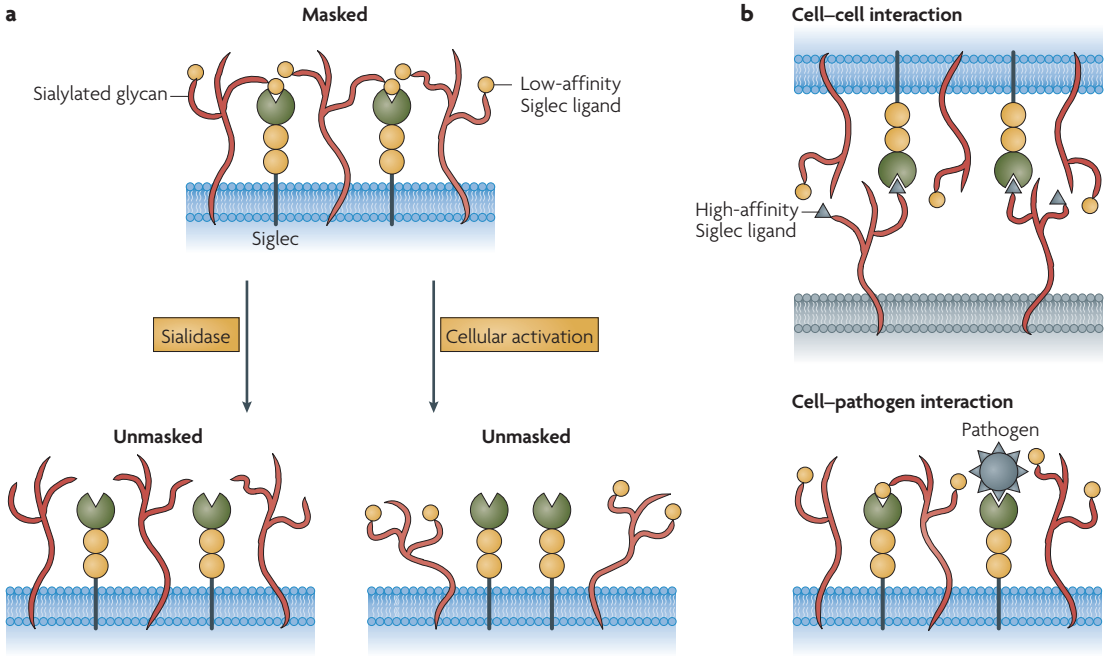


Figure 4 | ***Cis* and *trans* interactions of Siglecs. a** | Most sialic-acid-binding immunoglobulin-like lectins (Siglecs) are masked at the cell surface owing to *cis* interactions with abundantly expressed sialic acids. Following exposure of cells to sialidase, which cleaves the *cis*-interacting Siglec ligands, or in some cases following cellular activation, Siglecs become unmasked, which allows them to make interactions with ligands in *trans*. **b** | Even when Siglecs are masked by *cis* interactions, *trans* interactions might occur during an encounter with another cell or a pathogen expressing higher affinity ligands that can out-compete the *cis* interactions.

there is minimal colocalization of CD22 with the BCR. Most of the CD22 molecules (~80%) are associated with clathrin domains, which is consistent with the presence of cytoplasmic tyrosine-based motifs for the clathrin adaptor protein AP50 (REF. 54). By contrast, the BCR is minimally associated with clathrin domains. Following B-cell activation, the BCR moves into activation rafts, which subsequently fuse with clathrin domains before they are endocytosed[86,87]. Because CD22 is excluded from activation rafts, it is probable that CD22 exerts its regulation of BCR signalling in the fused raft/clathrin domains[34,55,86,87]. In ligand-deficient mice, there is no change in the localization of CD22. However, the amount of cell-surface IgM that is colocalized with CD22 increases twofold (from 20–25% to 40–50%), which is associated with a dramatic shift in the distribution of IgM to the raft/clathrin domains. This shift in BCR localization also results in increased endocytosis and reduced half-life of IgM[35,55]. The redistribution and reduced half-life of IgM do not occur in mice deficient in both CD22 and ST6GAL1, indicating they are mediated by CD22, and are not due to another effect of the ST6GAL1 deficiency. So, for ligand-deficient mice, the increased colocalization of the BCR and CD22 in fused raft/clathrin domains of resting B cells probably accounts for the reduced BCR signalling mediated by CD22 (FIG. 5). These results also indicate that *cis* ligands of CD22 reduce BCR localization in raft/clathrin domains of resting B cells of wild-type mice by an as-yet-undefined mechanism.

In addition to the effect on BCR signalling, deficiency in CD22-ligand binding leads to reduced levels of cell-surface CD22 and IgM, increased apoptosis and B-cell turnover, and a reduction in the number of marginal-zone B cells[84]. These properties are also observed in CD22-deficient mice, which suggests that they are regulated by CD22–ligand interactions[35,55,84,85,88]. So, it is probable that other important roles of both *cis* and *trans* ligands in CD22 function are likely to be revealed using appropriate mouse models.

Functions mediated by CD33-related Siglecs

The CD33-related Siglecs are mainly expressed by mature cells of the innate immune system, such as neutrophils, eosinophils, monocytes, macrophages, NK cells, DCs and mast cells (FIG. 1). CD33 itself is well known as a marker of myeloid progenitor cells, indicating a potential role for CD33 in the regulation of cellular proliferation and/or differentiation. Other CD33-related Siglecs seem to be expressed at later stages of haematopoiesis[89–91]. Numerous studies point to important roles of CD33-related Siglecs in modulating leukocyte behaviour, including inhibition of cellular proliferation[92,93], induction of apoptosis[94,95], inhibition of cellular activation[96–100], induction of pro-inflammatory cytokine secretion[101] and, in the case of Siglec-H on plasmacytoid DCs (pDCs), suppression of interferon-α (IFNα) production[13]. In general, these functions have been defined using selected Siglecs (FIG. 6) and the extent to which they can be extrapolated to the other CD33-related Siglecs is unknown. The signalling pathways are poorly understood but in most cases are assumed to involve the ITIM and ITIM-like motifs and recruitment of tyrosine phosphatases (FIG. 6).

Rafts or activation rafts
Membrane microdomains enriched in glycosphingolipids, where cell signalling receptors form macromolecular complexes with other proteins involved in the initiation of cell-activation pathways.

Table 1 | **Interactions between pathogens and Siglecs**

Pathogen	Pathogen sialic-acid ligand	Host Siglecs	Result of Siglec binding	References
PRRSV	Unknown. Viral membrane glycoprotein(s)?	Sialoadhesin	Pathogen endocytosis and productive infection	59
Neisseria meningitidis	Neu5Acα2–3Gal in lipo-oligosaccharides	Sialoadhesin, Siglec-5	Increased pathogen uptake by macrophages	60
Campylobacter jejuni	Neu5Acα2–8Neu5Acα2–3Gal in lipo-oligosaccharides	Siglec-7	Increased pathogen binding to NK cells and monocytes	62
Trypanosoma cruzi	Neu5Acα2–3Gal in mucins	Sialoadhesin	Increased pathogen uptake by macrophages	61
Group B *Streptococcus*	Neu5Acα2–3Gal in polysaccharides	Multiple CD33-related Siglecs	Unknown	63

Gal, galactose; Neu5Ac, *N*-acetylneuraminic acid; PRRSV, porcine reproductive and respiratory syndrome virus; Siglec; sialic-acid-binding immunoglobulin-like lectin.

Paralogue
Paralogy describes homologous genes in a single species that diverged by gene duplication. Paralogues are more likely to evolve new functions. Siglec-F and Siglec-8 are unusual in that they are paralogues that have developed similarities in cell-type expression and binding specificity by convergent evolution.

It should be emphasized that many of these studies have been carried out using Siglec-transfected cells and/or antibody crosslinking of cell-surface proteins, and the activities need to be confirmed in more physiological systems.

An important function of CD33-related Siglecs is their ability to regulate cell growth and survival, either by inhibition of proliferation or induction of apoptosis. Inhibition of proliferation was first shown for CD33 and Siglec-7 using both normal haematopoietic cells and myeloid leukaemic cells[92,93], and it was recently confirmed using transfected Ba/F3 cells[102,103]. With the Ba/F3 cells, inhibition of cytokine-dependent proliferation depended on crosslinking Siglecs with primary and secondary antibodies and required an intact ITIM[102,103]. Induction of apoptotic and non-apoptotic cell death has been shown for human eosinophils and neutrophils through antibody-induced ligation of Siglec-8 and Siglec-9, respectively[94,95]. Interestingly, cell-death induction by these Siglecs is enhanced in the presence of cytokines that normally promote survival, which suggests a complex interplay between cytokine receptor and Siglec signalling pathways[104]. Regulation of ITAM-dependent cellular activation by CD33-related Siglecs has been shown in various cell types, including transfected T cells, mast cell lines and myeloid cell lines. Interestingly, both primary human T cells and Jurkat cells, which normally lack significant levels of CD33-related Siglecs, showed inhibition of T-cell-receptor-dependent activation following overexpression of Siglec-5, Siglec-7 or Siglec-9 (REFS 99,105). In comparison, chimpanzee T cells express several CD33-related Siglecs and this may account for their lower proliferative responses compared with human T cells[105].

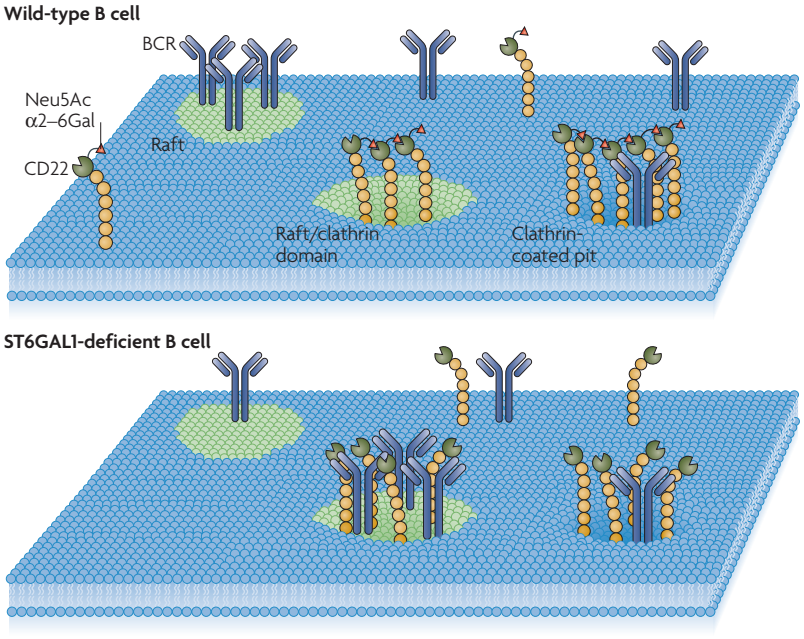


Figure 5 | ***Cis* ligands of CD22 influence microdomain localization of the B-cell receptor.** In resting B cells, CD22 is mainly localized in clathrin-coated pits, whereas the B-cell receptor (BCR) shows minimal association with these microdomains. In the absence of CD22-ligand binding (such as in ST6GAL1-deficient mice), the BCR shows increased colocalization with CD22, which is coincident with the reduction of BCR signalling. This mainly occurs in fused raft/clathrin domains that typically form following BCR ligation before endocytosis of the BCR.

The most direct evidence for a role of CD33-related Siglecs in the modulation of leukocyte functions has been provided by studies of mice lacking Siglec-F[107], which is a functionally convergent paralogue of human Siglec-8 and is expressed by eosinophils[23,106] and by activated T cells. In a model of induced lung allergy, these mice show increased bone-marrow, blood and tissue eosinophilia, which is consistent with an inhibitory role of CD33-related Siglecs in controlling leukocyte expansion during inflammatory responses[107]. Taken together, these data indicate the possible existence of a negative-feedback loop that controls allergic responses of eosinophils and helper T cells, through Siglec-F and upregulated expression of Siglec-F ligands in the inflamed tissue.

CD33-related Siglecs can also function as endocytic receptors that could be important in the clearance of sialylated antigens and/or in promoting or inhibiting antigen presentation[90,91,108–110]. Their endocytic capacity can also be exploited for therapy. For example, gemtuzumab ozogamicin (Mylotarg; UCB and Wyeth-Ayerst Laboratories (Wyeth)) is a humanized CD33-specific monoclonal antibody coupled to the potent antibiotic calicheamicin-γ_1, which is currently being used for the treatment of relapsed acute myeloid leukaemia (AML) following chemotherapy. Recent screens of CD33-related

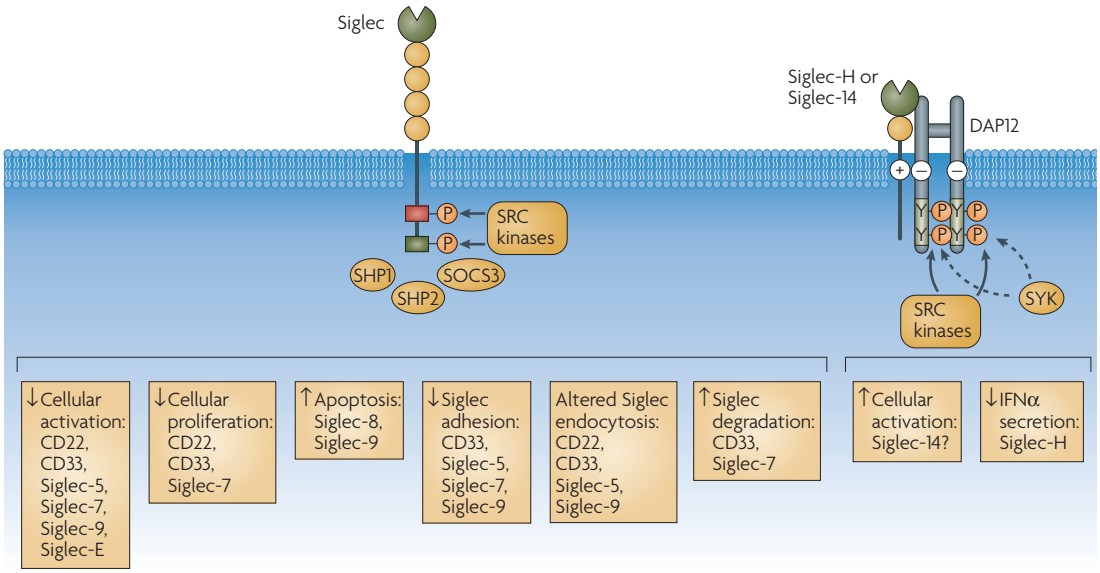


Figure 6 | **Signalling mediated by CD22 and the CD33-related Siglecs.** On phosphorylation of cytoplasmic tyrosine-based signalling motifs by SRC-family tyrosine kinases, sialic-acid-binding immunoglobulin-like lectins (Siglecs) recruit and activate SRC homology 2 (SH2)-domain-containing proteins, notably the tyrosine phosphatases SHP1 (SH2-domain-containing protein tyrosine phosphatase 1) and SHP2 or the SOCS3 (suppressor of cytokine signalling 3) protein. This initiates a range of functional activities that are indicated for the Siglecs listed. In the case of Siglecs without cytosolic signalling motifs, charge-dependent transmembrane region interactions with DAP12 can provide ITAM (immunoreceptor tyrosine-based activation motif)-based signalling functions that are typically initiated by the recruitment and activation of spleen tyrosine kinase (SYK). ↑, increased; ↓, decreased; IFNα, interferon-α.

Siglec expression by AML cells have shown that several are expressed at variable levels and may therefore provide additional targets for the treatment of haematological diseases[90,91].

Signalling by CD33-related Siglecs. Most CD33-related Siglecs have two conserved cytoplasmic tyrosine-based motifs, comprising a membrane-proximal ITIM and a membrane-distal ITIM-like motif (consensus sequence (Glu/Asp)-Tyr-X-Glu-(Val/Ile)-(Arg/Lys); where X denotes any amino acid) (FIG. 1). The distal motif was originally described[111] as being similar to a signalling motif in the SLAM (signalling lymphocytic activation molecule) family[112] of receptors that recruit SAP (SLAM-associated protein) and/or its homologue EAT2 (Ewing's sarcoma-associated transcript 2). However, more recent studies on the consensus sequence for SAP and EAT2 binding (Thr-Ile-Tyr-X-X-(Val/Ile))[112] make it seem unlikely that CD33-related Siglecs interact with these adaptors. Mutagenesis experiments with CD33-related Siglecs have shown that the ITIM dominates over the ITIM-like motif, both for the recruitment of SHP1 and SHP2 and for inhibitory signalling functions[96–98,100,113,114]. However, the ITIM-like motif was required for optimal recruitment of SHP1, but not of SHP2, and could therefore be important in fine-tuning downstream signalling from CD33-related Siglecs.

The ITIMs of CD33-related Siglecs are important for other functions, including the suppression of Siglec-dependent adhesion to sialylated ligands and endocytosis[91,98,100,110,113]. The degree of tyrosine phosphorylation is likely to be crucial in determining which function predominates. Robust binding to SHP1 and SHP2 requires tyrosine phosphorylation of both the ITIM and ITIM-like motif. However, following mutation of both tyrosines to alanine, Siglec-5 was capable of weak SHP1 binding and activation and was still a potent inhibitor of cellular activation[100]. By contrast, mutation of the ITIM alone reversed the suppression of Siglec-dependent adhesion and this correlated with the loss of SHP2 binding[98,100].

Orr *et al.* have recently shown that suppressor of cytokine signalling 3 (SOCS3) can bind efficiently to the phosphorylated ITIMs of CD33 and Siglec-7 and compete with SHP1 and SHP2 for ITIM-dependent inhibition of cytokine-induced proliferation[102,103]. Recruited SOCS3 was shown to function as an E3 ligase, leading to proteasome-dependent degradation of both Siglec and SOCS3. As SOCS3 is a key negative regulator of cytokine signalling in myeloid cells[115], CD33–SOCS3 interactions could affect both SOCS3 and Siglec-dependent inhibitory functions. Taken together, these findings indicate a finely balanced mechanism of leukocyte activation and growth regulation involving CD33-related Siglecs, SHP1, SHP2 and SOCS3 proteins (FIG. 6).

Siglec-H is coupled to DAP12. Siglec-H is a CD33-related Siglec that is expressed by mouse and rat pDCs[13,109,116]. This receptor can mediate endocytosis and cross-presentation of antigens[109] and can also function as a negative regulator of IFNα production by pDCs[13]. This observation is surprising because Siglec-H lacks ITIM-like motifs and depends on the presence of the ITAM-containing adaptor DAP12 for cell-surface expression[13]. However, there

Suppressors of cytokine signalling 3
(SOCS 3). A member of the family of eight cytoplasmic proteins (SOCS1–SOCS7 and CIS) that contain an amino-terminal region of variable length, a central SH2 domain and a carboxy-terminal SOCS box. SOCS proteins provide a negative-feedback loop to attenuate signal transduction from cytokine receptors that act through the JAK–STAT (Janus kinase –signal transducer and activator of transcription) pathway.

Cross-presentation
The initiation of a $CD8^+$ T-cell response to an antigen that is not present within antigen-presenting cells (APCs). This exogenous antigen must be taken up by APCs and then re-routed to the MHC-class-I pathway of antigen presentation.

Paired receptors
These are membrane proteins, one of which is potentially inhibitory and the other activating and which are highly related to each other in the extracellular domain but differ significantly in the transmembrane and cytoplasmic regions.

is growing evidence that under certain circumstances ITAM-associated receptors can mediate inhibitory signalling through poorly characterized mechanisms[15]. So far, Siglec-H has not been shown to bind sialic acids[109], and the rat orthologue has a mutation in the arginine residue that is required for sialic-acid binding[10]. Strictly speaking, therefore, Siglec-H may not fulfil the criteria to be defined as a *bona fide* Siglec[117]. One interesting possibility is that this pDC-restricted receptor has evolved from sialic-acid binding to function as a pattern-recognition molecule that binds viral or other pathogen ligands and delivers them to endosomal compartments for subsequent triggering of Toll-like receptor (TLR)-dependent cytokine responses and antigen presentation[118]. So far, there are no reports addressing the possibility that the more conserved C2-set immunoglobulin domains of CD33-related Siglecs might mediate protein–protein interactions that are important in immune functions.

Siglec-5 is paired with Siglec-14, a DAP12-coupled receptor. Several inhibitory receptors of the immune system are paired with activating counterparts that share highly related extracellular domains but differ in the transmembrane and cytoplasmic regions. Paired activating receptors often have a positively charged residue within the transmembrane region that is required for binding to the ITAM-containing adaptors, such as DAP12 and the Fc receptor γ-chain, or to the DAP10 adaptor that contains the sequence Tyr-X-X-Met (where X is any amino acid), which recruits PI3K[119]. As shown for the NK-cell receptor Ly49H, which binds the MHC-like protein m157 of mouse cytomegalovirus[120,121], some paired activating receptors may have evolved as a counter-strategy to bind host-derived pathogen ligands. Although Siglecs were not previously thought to include paired receptors, recent data indicate that the inhibitory receptor Siglec-5 is paired with a putative activating receptor, Siglec-14, and both seem to be expressed by myeloid cells in a coordinated manner[14]. These proteins share more than 99% sequence identity in their first two immunoglobulin domains and then diverge in the rest of their coding sequences. Siglec-14 has an arginine residue in its transmembrane region that is required for its association with DAP12 (REF. 14). Siglec-5 and Siglec-14 would therefore be expected to deliver opposing signals through ITIM- and ITAM-dependent pathways, respectively. A different arginine residue (of the first immunoglobulin domain) that is required for sialic-acid recognition by both Siglec-5 and Siglec-14 is present in humans (but is mutated in almost all great-ape alleles), indicating that these two proteins may work in a cooperative manner, balancing activating and inhibitory signalling through sialic-acid recognition[14]. Indeed, repeated gene-conversion events occurred between the 5′ regions of the *Siglec5* and *Siglec14* genes in each primate lineage, assuring maintenance of a paired receptor status for sialic-acid binding.

Concluding remarks

Siglecs are emerging as important regulators of the immune system. What links this family of proteins at a molecular level is their ability to bind sialic acids in a range of glycoconjugates, both in *cis* and in *trans*. Challenges for the future are to understand in precise terms which ligands and counter-receptors are important for mediating the biological functions of Siglecs, to elucidate the role of sialic-acid recognition in Siglec biology and to dissect the signalling pathways that are triggered. Siglecs are also recognized as endocytic receptors and this function is likely to be regulated by the same tyrosine motifs that regulate signalling. The interplay between the regulation of receptor signalling and endocytosis may prove to be a fruitful area of investigation for the future. A related challenge will be to understand the impact of pathogen sialylation on Siglec-mediated host immune responses, an issue that may give insights into the evolutionary pathways that have led to the diversification of this family. With growing data linking inhibitory receptor polymorphisms and autoimmune disease, studies of Siglec polymorphisms among human populations are clearly warranted. Finally, the development of Siglec-specific agonists and antagonists may provide new approaches to the treatment of certain autoimmune and inflammatory conditions.

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Acknowledgements
Work in the authors' laboratories is supported by grants from the Wellcome Trust (P.R.C.) and the National Institutes of Health, USA (J.P. and A.V.). We are grateful to T. Angata for communicating details of Siglec-15 ahead of publication and to H. Attrill for assistance in preparing Figures 2c and 2d.

Competing interests statement
The authors declare no competing financial interests.

DATABASES
The following terms in this article are linked online to:
Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
CD22 | CD33 | MAG | Sialoadhesin | Siglec-5 | Siglec-7 | Siglec-8 | Siglec-9 | Siglec-11 | Siglec-F | Siglec-H | ST6GAL1

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