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Review

Therapeutic Targeting of Siglecs using Antibody- and Glycan-Based Approaches

Takashi Angata,[1] Corwin M. Nycholat,[2] and Matthew S. Macauley[3,*]

The sialic acid-binding immunoglobulin-like lectins (Siglecs) are a family of immunomodulatory receptors whose functions are regulated by their glycan ligands. Siglecs are attractive therapeutic targets because of their cell type-specific expression pattern, endocytic properties, high expression on certain lymphomas/leukemias, and ability to modulate receptor signaling. Siglec-targeting approaches with therapeutic potential encompass antibody- and glycan-based strategies. Several antibody-based therapies are in clinical trials and continue to be developed for the treatment of lymphoma/leukemia and autoimmune disease, while the therapeutic potential of glycan-based strategies for cargo delivery and immunomodulation is a promising new approach. Here we review these strategies with special emphasis on emerging approaches and disease areas that may benefit from targeting the Siglec family.

Trends

Siglecs are attractive therapeutic targets due to their restricted expression pattern.

The endocytic and immunomodulatory properties of Siglecs can be exploited.

Numerous antibody-based therapies targeting Siglecs are in clinical development.

Glycan ligands of Siglecs are effective for cargo delivery and functional modulation.

The Siglec Family of Immunomodulatory Receptors

The **Siglec** family comprises 15 family members in humans that are expressed on a restricted set of cells in the hematopoietic lineage, with several notable exceptions such as Siglec-4/myelin-associated glycoprotein (MAG) on oligodendrocytes and Schwann cells and Siglec-6 on placental trophoblasts (Figure 1) [1–3]. Through their outermost N-terminal V-set domain, Siglecs recognize sialic acid-containing glycan ligands on glycoprotein and glycolipids with unique, yet overlapping, specificities. Recognition of their ligands can affect cellular signaling through **immunoreceptor tyrosine-based inhibitory motifs** (ITIMs; see Glossary) on their cytoplasmic tails. For most Siglecs, these ITIMs have the capacity to recruit phosphatases; therefore, these members are referred to as inhibitory-type Siglecs. Exceptions to this are Siglec-1 and MAG, which lack such a motif, and the activatory-type Siglecs (Siglecs-14–16), which are associated with immunoreceptor tyrosine-based activatory motif (ITAM)-bearing adapter proteins through a positively charge amino acid in their transmembrane region. There are numerous ways in which the engagement of Siglecs with their ligands imparts a physiological response, which have been recently reviewed elsewhere [1].

Siglecs as Therapeutic Targets

The restricted expression pattern of Siglecs makes this family candidate targets for developing therapeutics for the treatment of a wide range of diseases. Nevertheless, it is worth noting that our knowledge of the expression patterns of human Siglecs – particularly recently discovered members – remains incomplete and some Siglecs are found in unexpected places [4–6], necessitating systematic studies. Moreover, the high expression of certain Siglecs on various lymphomas and leukemias has made them obvious targeting candidates [7–9]. However, several additional features of the Siglecs make them particularly well suited for targeting in

[1]Institute of Biological Chemistry, Academia Sinica, Taipei, Taiwan
[2]Department of Cell and Molecular Biology, The Scripps Research Institute, La Jolla, CA, USA
[3]Department of Chemical Physiology, The Scripps Research Institute, La Jolla, CA, USA

*Correspondence: mmacaule@scripps.edu (M. Macauley).

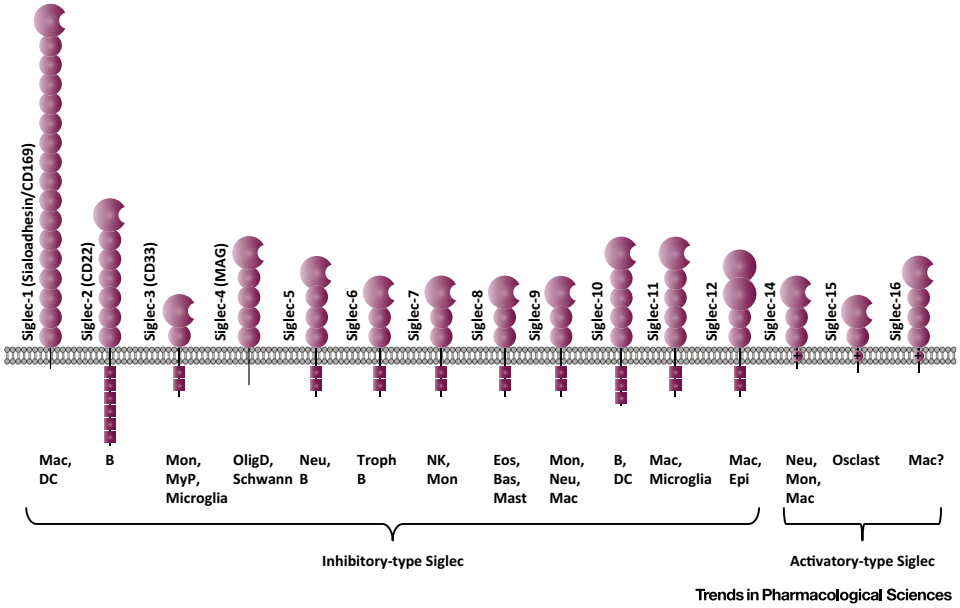

Figure 1. The Family of Human Siglecs. Differences between family members include the number of extracellular immunoglobulin domains, the number of intracellular immunoreceptor tyrosine-based inhibitory motifs (ITIMs), the presence of a positively charged intramembrane residue (Siglecs-14–16), and loss of sialic acid recognition (Siglec-12). Inhibitory-type and activatory-type Siglecs are noted. Expression patterns for each Siglec in normal individuals are indicated below. Abbreviations: Mac, macrophage; B, B cell; Mon, monocyte; MyP, myeloid precursor; OligD, oligodendrocyte; Neu, neutrophil; Troph, trophoblast; NK, natural killer cell; Eos, eosinophil; Bas, basophil; Mast, mast cell; DC, dendritic cell; Epi, epithelial cell; Osclast, osteoclast.

disease. One important attribute is that most of the Siglecs are rapidly endocytosed on engagement with antibodies [10–14] or glycan ligands [15–18]. For certain Siglecs, it has been shown that they undergo constitutive endocytosis and recycle back to the cell surface [10,19], although it remains to be determined whether this recycling feature is common to the entire Siglec family. Also unresolved is whether the endocytic properties of Siglecs are integral to their natural functions, partly because the endocytosis depends on the sequence motif nested in ITIM and thus mutagenesis will affect both the signaling and endocytic properties of Siglecs. Regardless, the endocytic properties of the Siglecs make them good targets for delivery of cargo to specific cell types. Another characteristic of Siglecs that makes them attractive therapeutic targets is their ability to modulate cellular signaling. Recently developed strategies aim to take advantage of this property to alter cell fate [20]. A growing body of work has shown that these therapeutically relevant properties of Siglecs can be exploited with antibody- and glycan-based targeting strategies. Here we review these strategies by comparing and contrasting the benefits of each strategy, describe diseases that are currently the focus of Siglec targeting, and highlight recent work that has indicated where Siglec targeting may find utility in the future.

Antibody-Based Targeting of Siglecs

Dating back to the 1980s, the high and selective expression of CD33 and CD22 on certain types of lymphoma and leukemia suggested that these Siglecs would be prime candidate targets to treat these cancers. Antibodies against CD22 and CD33 continue to be explored as potential therapeutics against B cell leukemia/lymphoma and acute myeloid leukemia (AML), respectively. In recent years, the antibody-based tools to target Siglecs have become more sophisticated (Figure 2) and the range of diseases considered as targets of therapeutic antibodies against Siglecs has expanded (Table 1).

Glossary

Antibody-dependent cellular cytotoxicity (ADCC): a component of the adaptive immune response and an important effector function of antibodies. Antibodies coating the surface of a target cell recruit effector cells (e.g., NK cells) that induce target cell lysis.

Complement-dependent cytotoxicity (CDC): part of the adaptive immune response involving complement activation. Antibodies coating the surface of a target cell recruit C1q, leading to activation of the classical pathway for complement activation and the formation of a membrane attack complex that induces target cell lysis.

Immunoreceptor tyrosine-based inhibitory motif (ITIM): tyrosine residues on the cytoplasmic tail of receptors are phosphorylated under the appropriate physiological circumstances. Phosphorylation creates a ligand for SH2 domain-containing proteins, thereby recruiting them to modulate immune cell activation.

***N*-acetylneuraminic acid (Neu5Ac):** a nine-carbon keto sugar that is the most prominent sialic acid found in mammals. Typically terminates glycans through α2–6, α2–3, or α2–8 linkages with the underlying carbohydrate residue. Installed on glycoproteins and glycolipids through the actions of the sialyltransferase family of glycosyltransferases.

Sialic acid-binding immunoglobulin-like lectin (Siglec): a family of 15 (in humans) cell-surface receptors expressed predominantly in the immune system that typically recognize sialic acid-containing glycoproteins and glycolipids as their ligands. Modulation of immune cell activation is mediated through either ITIMs in their cytoplasmic domain or through positively charged residues in their transmembrane domain that mediate pairing with activatory coreceptors. Several Siglecs do not have either an ITIM or a positively charged transmembrane but remain capable of modulating cellular activation.

Siglec-engaging tolerance-inducing antigenic liposomes (STALs): liposomes that co-display an antigen and high-affinity Siglec ligand. Co-presentation recruits CD22 to the BCR on the surface of B cells,