Design of Glycopolymers for Controlling the Interactions with Lectins

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REVIEW

Design of Glycopolymers for Controlling the Interactions with Lectins

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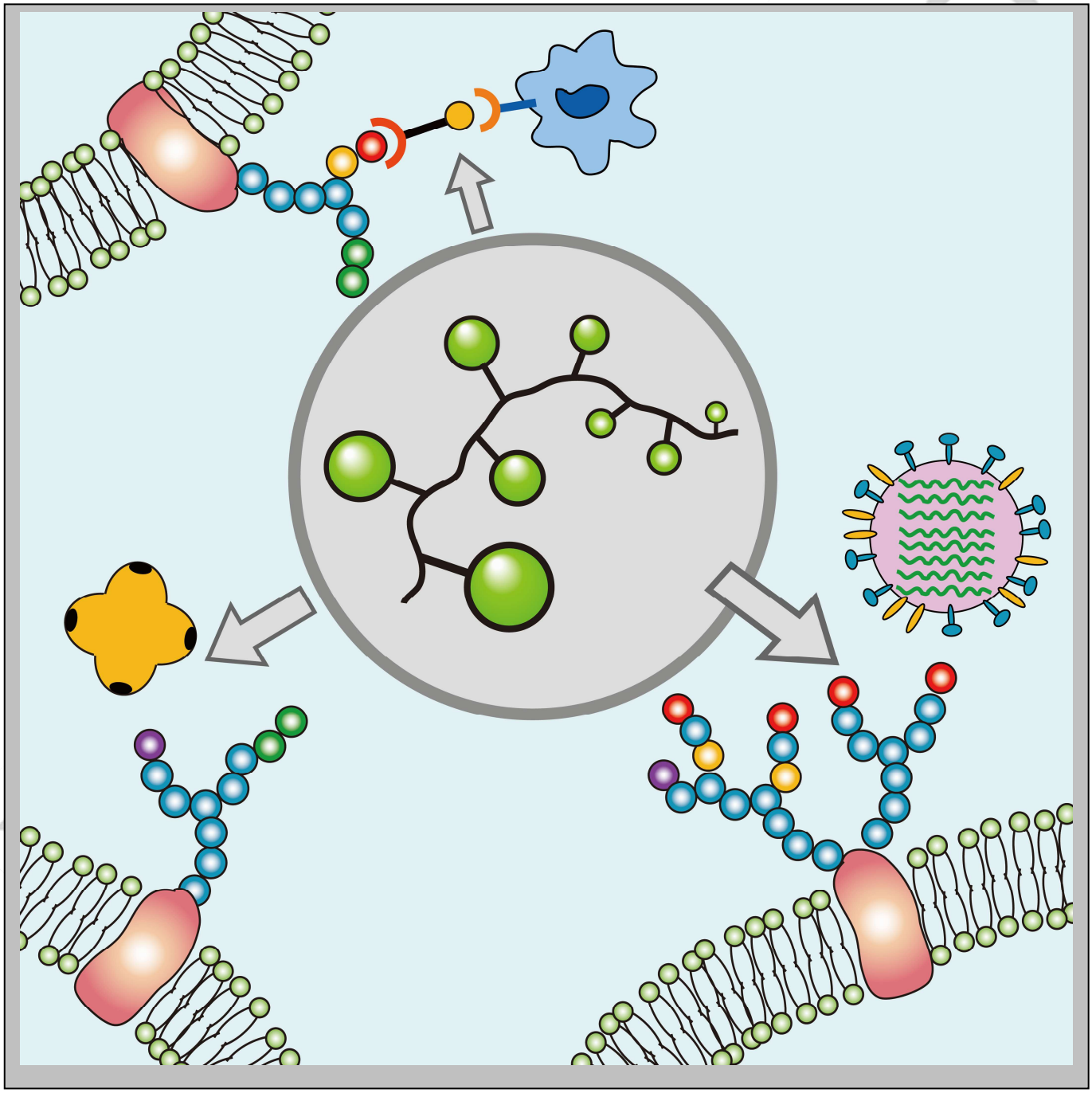
Dedication ((optional))



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Abstract: Carbohydrates are involved in life activities through the interactions with their corresponding proteins (lectins). Pathogen infection and the regulation of cell activity are controlled by the binding between lectins and glycoconjugates on cell surfaces. A deeper understanding of the interactions of glycoconjugates has led to the development of therapeutic and preventive methods for infectious diseases. Glycopolymer is one of the classes of the materials present multiple carbohydrates. The properties of glycopolymers can be tuned through the molecular design of the polymer structures. This review focuses on research over the past decade on the design of glycopolymers with the aim of developing inhibitors against pathogens and manipulator of cellular functions.

1. Introduction

Carbohydrates are an important energy source for life; however, the role of carbohydrates is not limited. Glycoligands on the cell surface are composed of various types of carbohydrates, and the interactions of the non-reducing terminals with lectins are involved in various physiological phenomena such as pathogen infection and cell–cell communication.[1] If the functions of these carbohydrates can be controlled by synthetic materials, it will greatly contribute to the biotechnology, such as development of drugs against new virus or immune diseases.[2] Thus, glycoengineering aims to artificially reproduce and adapt the functions of various carbohydrates by using carbohydrate or carbohydrate mimics.[3] Carbohydrates bind to the binding pockets of their corresponding proteins (lectins). Lectins are defined as carbohydrate binding proteins and exist in living organisms, ranging from viruses and bacteria to plants and animals.[4,5] The specificity of the interaction between the lectin and the carbohydrate is called “carbohydrate recognition”.[4,5] Although the affinity of free (not clustered) saccharides for carbohydrate recognition domains (CRDs) is generally weak (K_d ≃ 10^{-3} M), the specificity of these interactions is high. The interaction between a carbohydrate molecule and a CRD depends on both the functional groups in the pyranose ring and the directions of the hydroxyl groups (axial or equatorial). A carbohydrate molecule has multiple hydroxyl groups, and hydrogen bonds to the side chains of polar amino acids are crucial for carbohydrate recognition. Moreover, it has also been hypothesized that the C-H groups of a carbohydrate molecule play an important role in the interaction, and recent studies have revealed the importance of CH–π interactions.[6] Studies on the interaction of carbohydrates with lectins are still underway to understand the detailed mechanism.

To compensate the weak interaction between a carbohydrate and a CRD, most of the lectins exhibit multivalent interactions *in vivo* (the cluster glycoside effect).[7] The lectins have a symmetrical structure and have multiple CRDs in the molecules. To exhibit the cluster glycoside effect, a molecule must present multiple glycounits. One of the classes of such multivalent glycomaterials is glycopolymer (Figure 1).[8–11] Synthetic glycopolymers can be easily produced by several steps of polymerization and can be combined with various functional groups.[12] Many glycopolymers have been developed along with the development of polymerization techniques, and their interactions with lectins have been studied.[13,14] In this review, we summarize the molecular designs of synthetic glycopolymers reported so far and their effects on their interactions with the lectins.

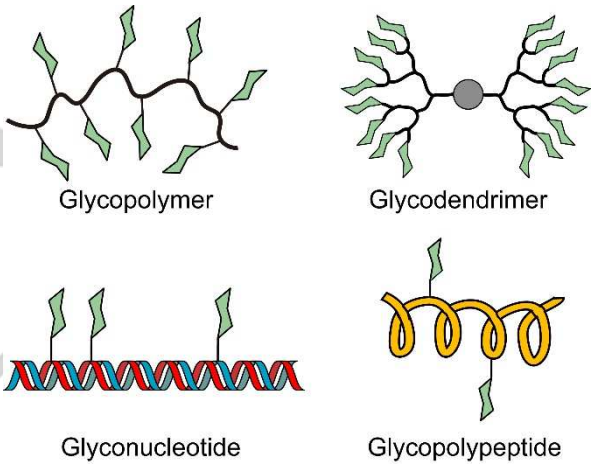

Figure 1. Illustrations of multivalent glycomolecules.

2. Lectins of Viruses and Bacteria

Lectins are involved in the infection of pathogens such as viruses and bacteria. Viruses have lectins on their surface and are taken up by binding to glycoconjugates on the cell surface.[15] In addition, in the case of bacteria, in addition to the behavior of being taken up into cells, toxin proteins that bind to glycoconjugates of cells may also be produced. This chapter summarizes the design of glycopolymers that bind to lectins related to such pathogens.

2.1. Hemagglutinin (HA)

Hemagglutinin is a homotrimeric lectin present on the surface of influenza viruses and has three CRDs on its surface. The glyco-structure containing sialic acid is the corresponding structures.[16] The viruses of human strain recognize the sialylated glycan receptors terminated by N-acetylneuraminic acid (Neu5Ac) α2→6 linked to galactose (Gal) (Neu5Ac-α(2,6)-Gal), which are primarily expressed on the apical surface of the human

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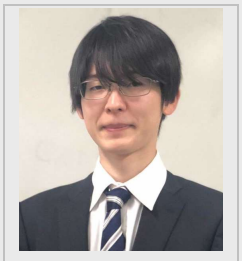

Prof. Yoshiko Miura received her B Eng. Degree in 1995 and PhD in 2000 from the Kyoto University under the supervision of Professor Shiro Koabayashi. She spent her postdoctoral period from 2000 to 2001 at the University of Pennsylvania in Professor Virgil Percec's group. In 2001, she joined the Department of Molecular Design and Engineering, Nagoya University, as Assistant Professor. In 2005, she was appointed Associate Professor at the Schools of Materials Science in Japan Advanced Institute of Science and Technology. In 2010, she was appointed Professor at the Department of Chemical Engineering, at Kyushu University. Her current research focuses on biopolymers based on precise polymer synthesis, and the development of new organic chemistry methods based on the materials science.

upper respiratory epithelium.[17] In contrast, the avian influenza viruses bind to Neu5Ac-α(2,3)-Gal. Synthetic glycomaterials containing sialic acids are expected to inhibit viral infection, and however, the binding constant of the one CRD and one sialic acid is weak (K_a = 10^3 M^{-1}).[18] Thus, it is necessary to enhance the interaction through multivalent effects, and many types of glycopolymers presenting multiple sialic acids have been reported. The representative study in the early stage was done by Whitesides and co-workers. They synthesized the glycopolymers based on the acrylamide main chains, and evaluated the interactins with the influenza virus by hemagglutination inhibition assay. [19–21] These works clarified the influence of the molecular weight of the polymers and the ratio of glycounits on the inhibition of the virus infection.

Since the latter half of the 1990s, "living" polymerization techniques have been developed, allowing the preparation of the controlled glycopolymers with defined structures.[22] Miura and co-workers synthesized acrylamide-type glycopolymers with sialyllactose trisaccharides as side chains by "post-click" chemistry.[23] The molecular weight and the ratio of the functional groups were controlled by reversible addition-fragmentation chain transfer (RAFT) polymerization, and sialyllactose was introduced as the side chains by copper-catalyzed azide-alkyne cycloaddition.[24] In this work, they revealed that both of the polymer length which is sufficient to form multivalent binding with hemagglutinin and of the appropriate glycounit density which avoid the steric hindrance of the trisaccharide side chains are important for the strong interactions with the influenza viruses. Furthermore, inspired by the research on glyco-ligands aiming to achieve the multivalent binding to the three CRDs of hemagglutinin using DNA and peptides,[25,26] our group synthesized tri-arm star glycopolymers.[27,28] Prior to the synthesis, the length of the star polymer chains was predicted using the Gaussian model of synthetic polymers, and the degree of polymerization required to achieve multivalent binding to the three CRDs of hemagglutinin was estimated (Figure 2).[28] The disance between the two CRDs of hemagglutinin is ca. 2.6 nm, and the corresponding degree of polymerization was 40. In the hemagglutination inhibition assay, the interaction of the star glycopolymer with the predicted structure was the strongest among the synthesized glycopolymers, suggesting effective multivalent binding to the influenza viruses. Tanaka and co-workers synthesized glycopolymers displaying sialyl-oligosaccharides (*N*-glycan) as the side chains by controlled polymerization.[29,30] The oligosaccharide has two sialic acid at the terminals of the structures, and showed strong interactions with the influenza vriruses although the incorporated ratio of the glycounits was not so high (< 10 mol%). This is owing to the local multivalent effects of *N*-glycan. Recently, Hartmann and co-workers synthesized the glycopolymers displaying sulfated mannose and galactose, mimicking the natural polysaccharide of heparin.[31] The glycopolymers have negative charge and effectively inhibited the viral infection. The effectiveness of the polyanionic polymers mimicking heparin or heparan sulfate for viral inhibition is gathaering attention.[32,33]

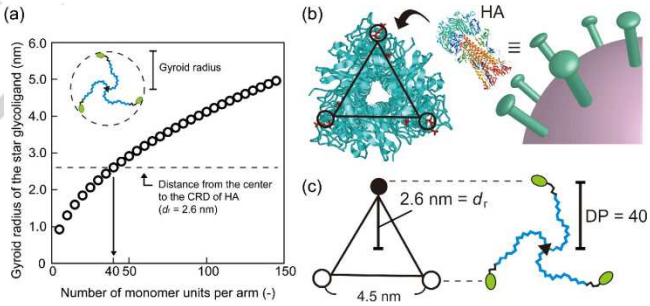

Figure 2. (a) Estimated gyroid radius of star glycopolymers with different numbers of monomer units per arm. (b) Structure of hemagglutinin (PDB: 5HMG) and surface illustration of the influenza virus. The amino acids involved in the interaction with sialic acids are shown in red. (c) Arrangement of the CRDs of hemagglutinin as a triangle (left) and the star glycopolymer with the appropriate DP (right). The circles indicate the CRDs on HA. The distance between two CRDs is 4.5 nm. The distance from the center to the CRD is 2.6 nm and is defined as d_r. Reprinted with permission from Ref. 28. Copyright 2022 American Chemical Society.

Godula and co-workers synthesized glycopolymers that mimic the mucin layer present on the cell surface for investigation of the roles in the viral infection.[34,35] In their works, lipid moieties were attached to the terminals of the glycopolymers aiming the insertion of the polymers onto the lipid bilayers of the viruses or cells. The transmission electron microscope (TEM) observation elucidated that the lipidated glycopolymers were inserted onto the

viral surface more effectively than those without lipid moiety (Figure 3).[34] Using this technique, they investigated the effectiveness of the physical barrier to restrict lectin and virus adhesion to target receptors.[35] Counterintuitively, increasing the density of the mucin mimetic enhanced retention of bound lectin and virus. This intersting findings greatly contributed to the analysis of the mechanism of how pathogens that bind to glycoconjugates utilize mucins in the infection steps on cells. Recently, the effectiveness of mucin-inspired glycopolymers has been demonstarted.[36,37] In addition to binding to hemagglutinin through glycounits, an unique study was also reported where a neuraminidase inhibitor (zanamivir) was copolymerized with sialyllactose to inhibit not only the viral cell infection but also viral release from the cells.[38]

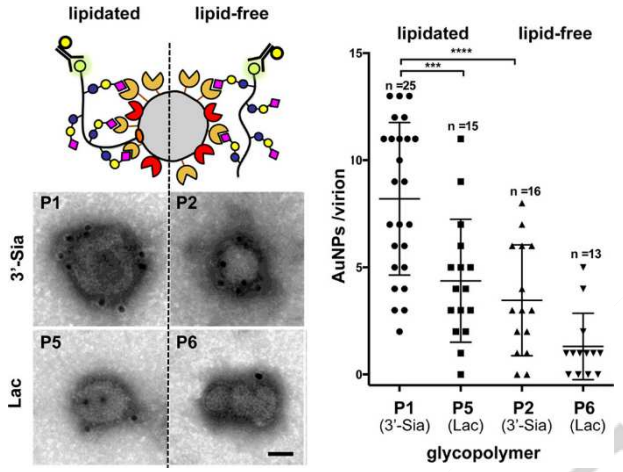

Figure 3. Incorporation of AF488-labeled decoys into the membranes of H1N1 virions was visualized by TEM after immunostaining with an anti-AF488 antibody conjugated with gold nanoparticles (Ab-AuNP, micrograph). The lipid anchor in polymers P1 and P5 promoted virion encapsulation, with precoordination of the sialoglycans in polymers **P1** and **P2** to the viral HA proteins providing additional enhancement. Reprinted with permission from Ref. 34. Copyright 2016 American Chemical Society.

2.2. Cholera Toxin B subunit (CTB)

The cholera toxin protein has the structure that contains two types of units, A and B. The B subunit is a homopentameric protein with a total of five CRDs. The natural ligand structure is monosialotetrahexosylganglioside (GM1), and the galactose and sialic acid moieties are involved in the binding.[39] The binding constant of CTB to GM1 is about 10^9 M^{-1}, which is relatively strong among carbohydrate–lectin interactions.[40] Although glycomaterials presenting multiple GM1 are considered to be effective CTB inhibitors, GM1 is expensive and difficult for total synthesis. Thus, alternative ligands for CTB have been desired. Gibson and co-workers reported that glycopolymers displaying galactose, which mainly contributes to the interaction of GM1 to CTB, and the secondary functional groups were effective ligands for CTB.[41,42] The secondary functional groups were hydrophobic groups such as aryl derivatives or usual carbohydrate (glucosamine). The localized structures with galactose and the secondary groups matched to the structure of CTB and allowed

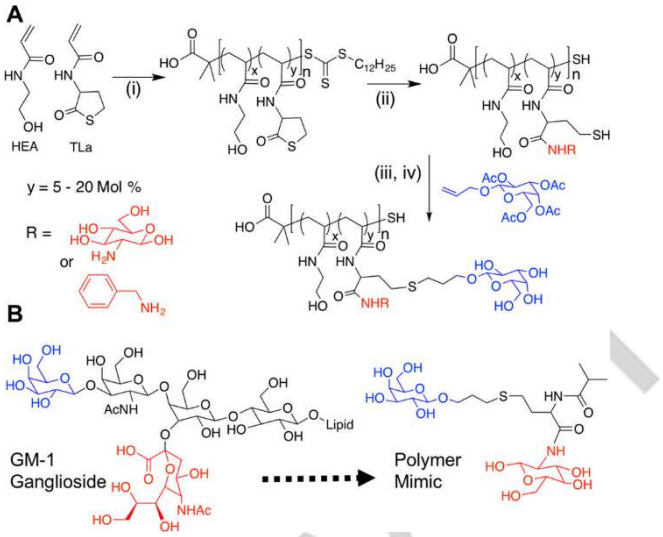

Figure 4. (A) Synthetic methodology. (i) RAFT polymerization, (ii) ring opening of thiolactone, and (iii, iv) thiol–ene click and deprotection. (B) Polymer design concept to mimic GM-1-branched structure. Reprinted with permission from Ref. 42. Copyright 2018 American Chemical Society.

the selective interactions with the target lectins (Figure 4). These works demonstrated that the common chemical moieties could substitute the glycomotif of GM1 (especially, the part of sialic acid).

Kobayashi and co-workers proposed a similar concept of mimicking the function of complex oligosaccharides with common carbohydrates. This is called as “carbohydrate module method”.[43] Our group applied this concept to synthesize glycopolymers that bind to CTB. The acrylamide-monomers bearing galactose or sialic acid units were copolymerized by RAFT polymerization. Surface plasmon resonance (SPR) measurement revealed that the glycopolymer displaying both of galactose and sialic acid units showed a stronger interaction with CTB than the polymers with either of them.[44] Furthermore, a combination with comprehensive polymer synthesis using photoinduced electron/energy transfer-RAFT (PET-RAFT) polymerization and SPR screening assay revealed that the glycopolymer composition containing 70 mol% galactose and 20 mol% sialic acid (and 10 mol% inert monomer) exhibited the strongest interaction among the polymer library (Figure 5).[45] This approach was also applied with the polymer structures displaying galactose and common hydrophobic residues.[46]

As another approach, Sampson and Yrlid et al. reported the glycopolymers displaying galactose and fucose for binding to CTB.[47,48] Although the original glyco-ligand for CTB is GM1, they targeted another binding site of CTB that binds fucose. In the inhibition assay of CTB infection, the glycopolymers containing galactose and fucose in the one molecule exhibited a stronger inhibitory ability than other polymers containing either of galactose and fucose, suggesting the expression of a cooperative interaction of the galactose and fucose units with CTB.

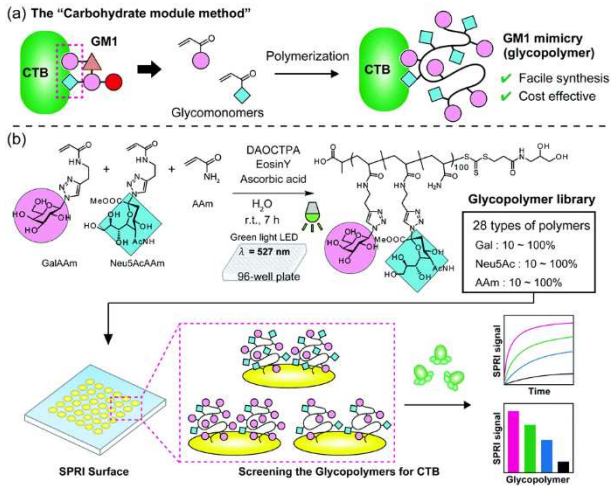

Figure 5. Schematic illustrations of the ''carbohydrate module method'' (a). Preparation of the glycopolymer library by PET-RAFT polymerization and screening of the library by SPRI (b). Reprinted with permission from Ref. 45. Copyright 2021 The Royal Society of Chemistry.

3. Lectins for transmembrane receptors on a cell membrane

Some lectins that recognize glycoconjugates exist on the cell surface as membrane proteins and are often involved in immune reactions.[49,50] In binding to glycoconjugates, the structures of transmembrane receptors slightly change, followed by cascading reactions in cells inducing various immune reactions. This chapter summarizes the design of glycopolymers that bind to lectins that exist on the cell surface and are involved in immune responses.

3.1. Dendric cell-specific ICAM-3 grabbing non-integrin (DC-SIGN)

DC-SIGN, also called the CD209 antigen, is a 44kDa type II transmembrane C-type lectin molecule with a CRD.[49] Like other C-type lectin family molecules, the extracellular domain of DC-SIGN molecule binds to mannose residues in a Ca^{2+}-dependent manner and plays an important role in primary immune responses for the following ligands: HIV-1 gp120 (HIV-1 capture and presentation to CD4+ T cells) and CMV envelope glycoprotein B (capture of CMV). Immature dendritic cells in peripheral tissues other than Langerhans cells, DC in lymphoid tissues, and specific macrophages express DC-SIGN.

Becer and Haddleton et al. reported pioneering work where they synthesized glycopolymers displaying mannose motifs by ATRP and evaluated their binding to DC-SIGN.[51] The several types of the glycopolymers with different sequences were prepared, and however, no significant effect of the polymer sequence was observed, demonstrating the difficulty of material design for enhancing the interaction with DC-SIGN. The Becer's group has designed the glycopolymers with specific structures such as star-shape or cyclic structures to control the glycodensity (Figure 6).[52,53] They achieved to decrease the binding dissociation constant to picomolar order.

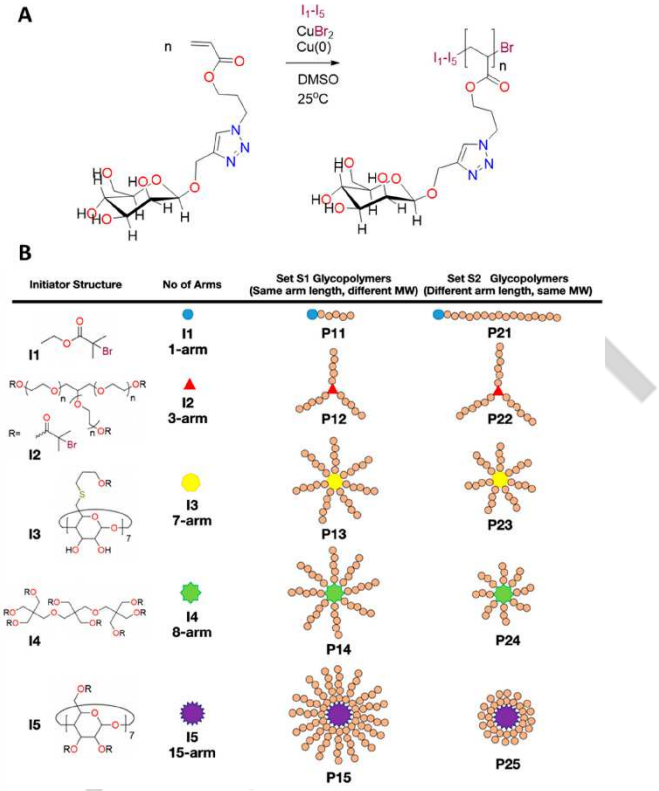

Figure 6. (A) Schematic representation for the Cu-mediated reversible deactivation radical polymerization (Cu-mediated RDRP) of mannose acrylate with different initiators. (B) Illustration of star initiators with different arms and glycopolymers with different structures. Reprinted with permission from Ref. 53. Copyright 2020 American Chemical Society.

The synthetic polymers prepared by radical polymerization have molecular distribution even with the controlled polymerization. Iterative exponential growth (IEG) synthetic strategy was proposed by Johnson and co-workers, which provides synthetic macromolecules with no dispersity for the structure.[54] This synthetic strategy was applied for investigation of the interactions of the precisely designed glycopolymers with human lectins.[55,56] The molecular weight, stereochemistry, and topology (linear or cyclic structure) were precisely controlled by IEG (Figure 7). Although there are several types of membrane proteins that bind to mannose residue, the glycopolymers with different structures showed the difference in the interactions with the lectins. The structural features mentioned above impacted the lectin binding, demonstrating that such molecular features must be considered in glycopolymer design.[55] Furthermore, these results have encouraged researches about the combination of synthetic polymers that mimics folded protein structures (SCNPs) and glycopolymers aiming design of the polymer functions.[57,58] Wang and co-workers reported the synthesis of ligand molecules with precisely controlled size and arrangement of the glycounits using a peptide backbone (polyproline). The interaction with DC-SIGN and Langerin, which is a membrane receptor like DC-SIGN, can be regulated and the glycoligand selectively bound only to DC-SIGN.[59]

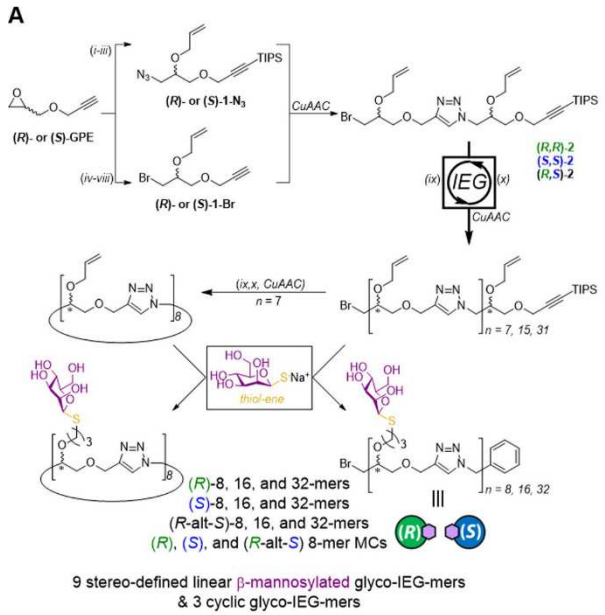

Figure 7. Synthesis of glyco-IEGmers. IEG strategy toward allyl-functionalized macromolecules and subsequent formation of β-mannosylated glyco-IEGmers. Reprinted with permission from Ref. 55. Copyright 2021 American Chemical Society.

3.2. Sialic acid immunobinding immunoglobulin-type lectin (Siglec)

Siglec is a cell surface protein that binds to sialic acid. It is a type I lectin found mainly on the surface of immune cells.[60–62] Fourteen species have been found in mammals, and they exert diverse functions based on cell surface receptor-ligand interactions. Many Siglecs have immunoreceptor tyrosine-based inhibition motifs (ITIMs) in their intracellular regions, which suppress immune cell activation. Upon ligand binding, Siglec recruits inhibitory proteins, such as Src homology region 2 (SH2) domain-containing phosphatases (SHPs), to her ITIM domain. After ligand binding, ITIMs are phosphorylated on tyrosines and serve as binding domains for SH2 domain-containing proteins such as SHP. This results in dephosphorylation of cytoplasmic proteins and inhibition of activation pathways. Tanaka and co-workers synthesized glycopolymers displaying α(2,8) disialic acids, which is the natural ligand for Siglec-7.[63,64] The multivalency of the glycopolymers enhanced the interaction of α(2,8) disialic acid with Siglec-7, indicating that the cluster glycoside effect is exhibited even though one Siglec molecule has only one binding site. Our group synthesized glycopolymers displaying 3'-sialyllactose and demonstrated the suppressed production of the NF-κB pathway in Siglec-expressing cells.[65] These reports demonstrate that glycopolymer with multiple glycounits is a promising material in targeting Siglec molecules.

Bertozzi and co-workers synthesized glycopolymers with sialyllactose derivatives on the side chains that bind strongly to Siglec-E.[66] They demonstrated that the insertion of the polymers onto the cell membrane by the hydrophobic moiety at the polymer terminus is important for the effective immunosuppression mediated through Siglec (Figure 8). The glycopolymer on the cell membrane enhanced the clustering of the multiple Siglec molecules, resulting in the better immunosuppression. In addition, the Bertozzi group demonstrated that the self-death mechanism of cells can be controlled by using such a glycopolymer.[67]

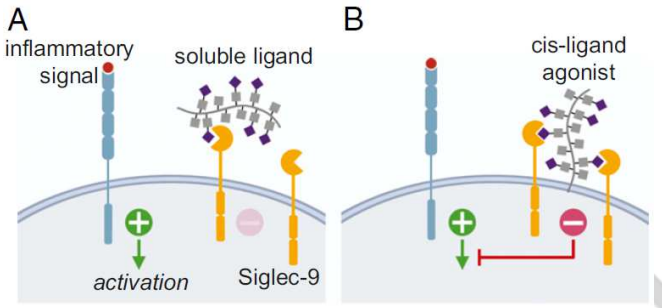

Figure 8. Lipid-tethered glycopolypeptides cluster and agonize Siglecs in cis on effector cells. (A) Immune cells express activating receptors that stimulate inflammatory signaling. (B) Clustering of Siglec-9 by cis-binding agonists stimulates inhibitory signaling that quenches activation Reprinted with permission from Ref. 66. Copyright 2021 National Academy of Sciences of the United States of America.

4. Summary and Outlook

This review focuses on relatively recent examples of the design of glycopolymers and their interactions with lectins. In recent years, attention has been paid to the emergence of new viruses such as SARS-Cov-2, and it is believed that some glycoconjugates are involved in their infection. A novel interaction system has also been discovered for receptors on cell membranes, and new compounds to control cell behavior are beginning to be explored.[68] In addition, due to the structure of polymers, it is possible to effectively combine with machine learning by treating monomers as units. The search for glycopolymers effective against unknown pathogens will greatly contribute to the fields of biochemistry and drug development.

Acknowledgements

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Keywords: Glycopolymers • Molecular recognition • Pathogen inhibitors • Lectins • Immune response

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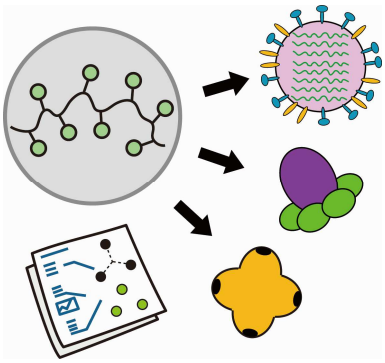

Carbohydrates are involved in our life activities through binding to corresponding lectins. Glycopolymer is one of the classes of the emerging materials in recent years that mimic the functions of the glycoconjugates on the cells. This review summarizes the research over the past decade on the design of glycopolymers with a focus on controlling the interactions with lectins.