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# Glycan–protein interactions in viral pathogenesis

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The surfaces of host cells and viruses are decorated by complex glycans, which play multifaceted roles in the dynamic interplay between the virus and the host including viral entry into host cell, modulation of proteolytic cleavage of viral proteins, recognition and neutralization of virus by host immune system. These roles are mediated by specific multivalent interactions of glycans with their cognate proteins (generally termed as glycan-binding proteins or GBPs or lectins). The advances in tools and technologies to chemically synthesize and structurally characterize glycans and glycan–GBP interactions have offered several insights into the role of glycan–GBP interactions in viral pathogenesis and have presented opportunities to target these interactions for novel antiviral therapeutic or vaccine strategies. This review covers aspects of role of host cell surface glycan receptors and viral surface glycans in viral pathogenesis and offers perspectives on how to employ various analytical tools to target glycan–GBP interactions.

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## Introduction

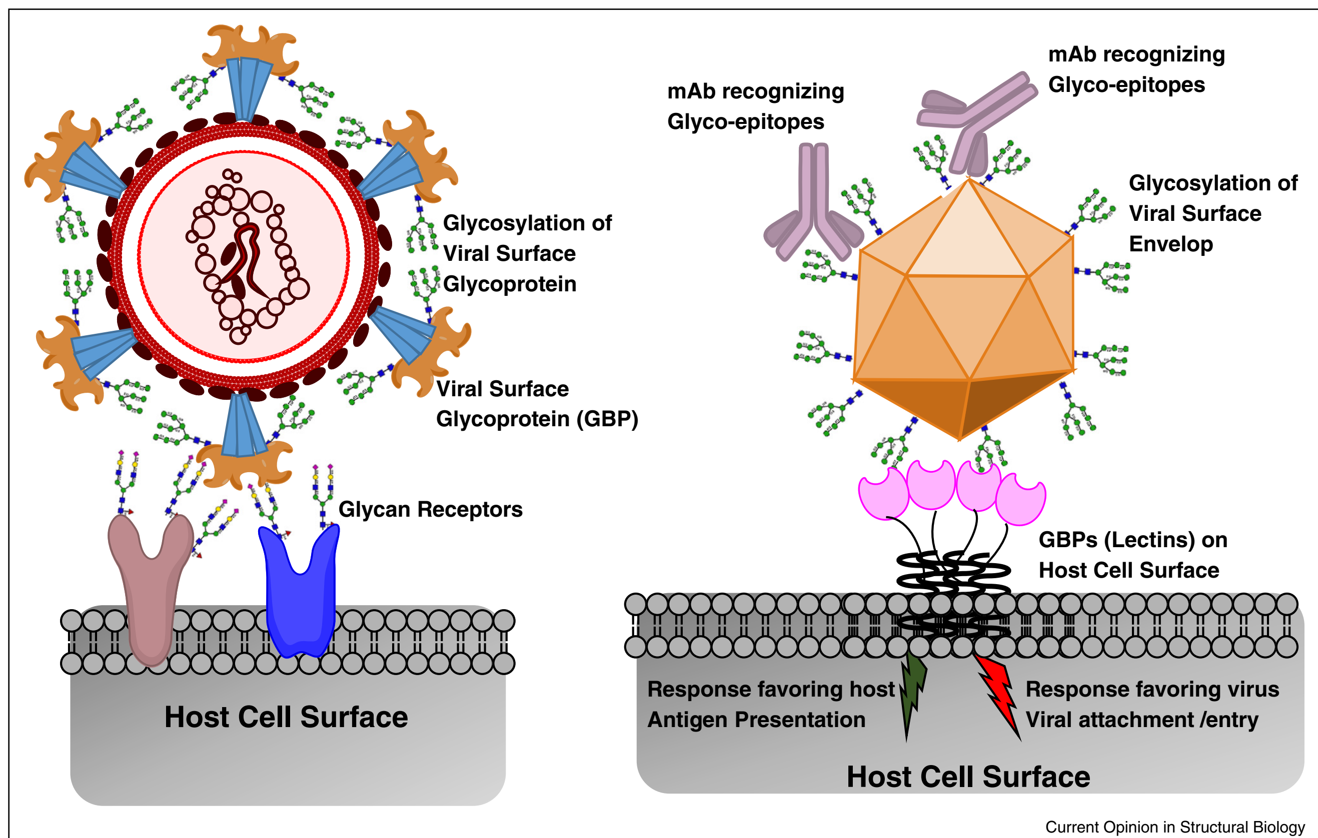
Complex glycans decorate surfaces of both host cells (and tissues) and viruses and play multifaceted roles in interactions between the viruses and host organisms that critically govern viral pathogenesis [1••,2•,3•,4]. These complex glycans are attached N-linked or O-linked to proteins as a part of post-translational modifications or attached to lipids. The complexity and structural heterogeneity of the glycans displayed on host cell/tissue surface and on viral surface glycoproteins predominantly arises from the complex non-template driven biosynthetic machinery of the host cell involving several enzymes that show tissue-specific expression patterns [5–7]. The interplay between the virus and the host involves interactions between two surfaces decorated by complex glycans. In addition to the glycans, a critical component involved in this interplay is a set of proteins known as glycan-binding proteins (GBPs) or lectins (Figure 1).

The GBPs involved in virus–host interplay mediated by glycans are typically anchored on the surfaces of cells (for example C-type lectins, Siglecs, etc. [1••,8] and viruses (envelop proteins or spike glycoproteins) [2•,3•,4]. The functional unit of GBP is often multimeric comprising of homo-oligomers of individual protein domains each having a glycan-binding site [1••]. Each glycan-binding site shows specific recognition to glycan motif or substructure of the complex glycan structure comprising of 2-5 sugars; however, the binding affinity for a given site to a glycan motif is typically low to moderate. The binding affinity and specificity are further enhanced through avidity and multivalency wherein multiple glycan motifs displayed on the surface bind to multiple glycan binding sites in the GBP oligomer unit [1••,9].

The complex glycans displayed on host cell surfaces typically act as attachment factors, co-receptors or primary receptors that are specifically recognized by the viral surface glycoproteins. For example, complex glycans terminated by α2-3 or α2-6-linked sialic acid (N-acetyl neuraminic acid) act as receptors for several different viruses [10•]. Linear sulfated glycosaminoglycans such as heparan sulfate act as co-receptors for a variety of viruses [11] including dengue virus [12,13], hepatitis C virus [14], and foot-and-mouth disease virus [15]. The predominant display of specific glycan motifs on surfaces of different cells and tissues contributes to the host restriction and cell/tissue tropism of the virus. As an example, the human upper respiratory epithelial surface predominantly display sialylated glycan receptors terminated by α2-6-linked sialic acid and these receptors are specifically recognized by hemagglutinin glycoprotein (HA) on surface of influenza A viruses that are known to infect and transmit via respiratory droplets in humans [4,16–18]. On the other hand, when influenza A viruses that are commensal or epizootic in birds infect humans, they typically affect deep lung and other tissues that predominantly display sialylated glycan receptors terminated by α2-3-linked sialic acid and are unable to transmit efficiently via respiratory droplets.

The glycans displayed on viral surfaces are posttranslational modifications of envelop proteins in viruses such as

Figure 1




Schematic of complex glycans in the interplay between virus and host. Shown in the figure (on the left) is a schematic of a virus surface glycoprotein (such as influenza A virus hemagglutinin) that recognized glycans on the host cell surface as their primary receptors for viral attachment and entry. The viral surface protein is in itself glycosylated and depending on the site of glycan occupancy, the glycosylation would impact the binding of this protein to the host-cell glycan receptor. Shown on the right is a schematic of glycan on the surface of virus envelop proteins (such as dengue) interacting with GBP anchored on the host cell. This interaction could either be beneficial for the virus wherein it plays a role in viral attachment and entry into a cell capable of promoting the productive infection or it could be beneficial to the host wherein antigen presenting cells could uptake the virus and prime the host immune response.

flaviviruses including dengue and zika virus or of glycoprotein spikes as observed in influenza A virus, Ebola virus, etc. These glycans are added to the viral glycoproteins as a part of the host–cell glycan biosynthesis upon viral replication in the host. In most cases, glycosylation sites on viral surface proteins are highly conserved since the glycans at these sites critically maintain the stability of these proteins and the viral particles as a whole. In addition to maintaining the stability of the viral particles, these glycans also play key roles in mediating infection of host cells by certain viruses such as dengue and Ebola viruses through specific interactions with GBPs (such as C-type lectins) displayed on the host cell surface [1••,19].

The complex glycans on the viral surface also play a key role in host immune response to counter the viral infection. While GBPs anchored on surfaces of host cells such as dendritic cells (DCs) play a role in viral entry, it also plays a dual role to enhance antigen presentation and processing for adaptive immune response [1••]. Sites of N-linked glycosylation are often positively selected during evolution of the virus in human host to increase glycans on the viral surface so as to present glycans that mimic self-antigens and mask the underlying protein epitope which in turn permits the virus to evade host immune response. In other cases, particularly with HIV, the clustering of glycosylation sites on the gp120 surface glycoprotein present novel glyco-eptiopes that do not mimic self-antigens and therefore lead to potent neutralization by antibodies that target these novel eptiopes across a broad spectrum of viral strains [20••]. This review covers some general concepts on role of host cell surface glycan receptors and viral surface glycans in viral pathogenesis. Some perspectives on developing the appropriate tools to define target glycan motifs on host cells or viral surface towards developing antiviral strategies is also presented.

## Glycans on host surface mediating viral entry, infection and tropism

The viral surface glycoproteins have evolved to specifically recognize distinct glycan motifs on the host cell surface and these specific interactions are one of the many factors that contribute to virus entry into specific host cells and host tissue tropism. Depending on the virus, the host cell surface glycans act as general attachment factors, co-receptors or primary receptors that mediate viral infection and entry.

Acidic glycans such as linear heparan sulfate glycosaminoglycan polysaccharides or branched glycans terminated by sialic acid displayed on cell surfaces in many instances play a role in attracting viruses based on their negative charge and serve as initial attachment factors to the host cell. Specifically, heparan sulfate by virtue of its chain length and distribution of sulfate groups has been implicated to play key role as attachment factor or co-receptors mediating the initial attachment of several viruses including HIV [21,22], enterovirus EV71 [23,24], echovirus E5 [25], coxsackievirus A9 and B3 strains [26,27], dengue virus [12,13] and Ebola virus [28]. An established example of specific modification in heparan sulfate that mediates virus entry is that of 3-O sulfation of the glucosamine that plays a critical role in specific interactions with herpes simplex virus [29–31].

Sialylated glycan receptors play a more directed role in mediating binding, attachment and entry of viruses into host cells [10•]. It has been demonstrated that enterovirus EV-D68 binds sialylated glycan receptors along the canyon of the viral surface and that this binding event causes significant conformational change in the viral envelop that displaces the fatty acid (also known as pocket factor which maintains structural stability of the envelop) and prepares the virus for infection [32,33]. Furthermore, it has been indicated that sialylated glycan receptors specifically in the context of O-linked glycans and glycolipids and not in the context of N-linked glycans mediate infection of EV-71 virus [34]. Picornaviruses including coxsackievirus A24 and EV-70 which cause severe conjunctivitis have been demonstrated to preferentially bind to α2-6-linked sialylated glycan receptors [35–39].

The influenza A virus is among the best studied viruses that are known to bind to host cell surface sialylated glycan receptors. The binding specificity of the viral surface hemagglutinin (HA) to sialylated glycan receptors on the host cell surface is one of many factors that critically govern adaptation of influenza to the human host. Avian virus HA binds with high specificity and affinity to glycans terminated by α2-3-linked sialic acid which are found in abundance in avian gut and lower respiratory tract of humans [40–42]. Human virus HAs possess characteristic glycan receptor binding properties; their HA predominantly binds with high affinity (or avidity) to glycan receptors terminated by α2-6-linked sialic acid, which are predominantly expressed in the upper respiratory epithelia of humans [40,43,44]. The human upper respiratory epithelium is the primary target site for infection of human-adapted viruses and is thought to be a prerequisite for efficient human-to-human transmission via respiratory droplets [4]. In addition to HA, influenza A virus surface also has an enzyme that cleaves sialic acid from both viral surface and host cell surface glycans to enhance productivity of infection, prevent self-aggregation of new virions that emerge from productive infection in a host cell [45,46]. In fact one of the earliest antiviral therapeutic strategies based on host cell surface glycan receptors was the design of sialic acid analogues (oseltamivir, zanamivir, etc.) to specifically bind to and inactivate the influenza A virus NA [47].

In addition to acidic glycans, neutral glycans such as histo-blood group antigens present on bodily secretions and also epithelial surface of the human intestine play a key role in mediating initial infection and entry of most norovirus genotypes. The characteristic motif among these histo-blood group antigens is a fucose α1-2 linked to galactose which is specifically recognized by protruding domain (P) of the viral capsid [48,49]. In fact, oligosaccharides in milk which also comprise of terminal α1-2 fucosyl glycan motif (similar to that in histo-blood group antigen) have been shown to have a potent inhibitory role in norovirus infection by serving as receptor decoys [50,51].

## Role of viral surface glycoproteins in pathogenesis

During the natural course of viral pathogenesis in different mammalian hosts including humans, the glycan biosynthetic machinery of the host cell also glycosylates the viral surface proteins. These viral surface glycans interact with the GBPs on the host cell. These interactions either favor the virus in terms of gaining entry to specific target cells that display the GBP or favor the host where the viral glycans are recognized by various circulating GBPs that mediate clearance of the virus or by anchored GBPs on antigen presenting cells that prime host immune response to target the viruses (see [1••] for a detailed review). The glycan motifs on the viral surface glycans can be classified into three broad categories: first, high mannose type; second, acidic (terminal sialylation) and three, neutral (not capped by sialic acid).

Some of the circulating GBPs in different hosts that help in viral clearance include collectins (recognize high mannose type and neutral glycans), surfactant proteins SP-A and SP-D (recognize high mannose and acidic glycans), mannose binding lectin, ficolins and galectins that show a broader diversity in recognition of high mannose, neutral and acidic glycans [1••,8]. Langerin is a C-type lectin on surface of Langerhans cells (antigen presenting cells) that

specifically recognize high-mannose type glycans on viral surface and plays a key role in priming the host immune response to recognize viral glycopeptides as antigens. A prototypic example of immune response targeted to viral surface glycans is that of HIV where numerous antibodies targeting the glyco-eptiopes achieve potent neutralization against a broad spectrum of viral strains [20••].

Among the GBPs on host cell surface that bind to viral surface glycans to facilitate viral entry and infection, the dendritic cell-specific ICAM-grabbing non-integrin (DC-SIGN) and liver/lymph node specific ICAM-grabbing non-integrin (L-SIGN) are the most prominent and play a key role in pathogenesis of numerous viruses including HIV, flaviviruses (dengue, zika), Ebola virus, measles virus, respiratory syncytial virus, coronavirus (SARS), etc. [1••,52]. In fact it has been demonstrated that the dengue virus switches its specificity from DC-SIGN (high mannose and fucosylated N-linked glycans) which plays a key role in infection of the primary monocyte cells to L-SIGN (stricter binding to high mannose glycans) during subsequent secondary infection of other cells including hepatocytes [53•,54,55].

In addition to their interactions with mammalian host GBPs, glycosylation of the viral surface proteins also impacts binding of these proteins to host cell glycan receptors as observed in the case of influenza A virus HA. Molecular dynamics simulation studies predicted that HA glycans may form interactions near the binding pocket to influence receptor binding [56]. Site-directed mutagenesis to knock-out glycosylation sites on HA or modifying structure of N-linked glycans on the virus by enzymatic treatment or transgenic cell lines have shown distinct changes in glycan-receptor binding specificity [57]. In the case of the 1918 pandemic H1N1 influenza viruses, a mutation that abrogates glycosylation at a single highly conserved site significantly impacted the ability of the virus to bind to α2-6 sialylated glycan receptors but not to α2-3 sialylated glycan receptors [58]. Site-specific loss-of-glycosylation mutations have also been shown to impact glycan receptor-binding specificity which in-turn governed virulence in mice [59–61]. Therefore, it is evident that the viral surface glycosylation governed by specific glycosylation sites and the structural heterogeneity of the glycans at each site in the relevant physiological context of virus interaction with the host cell has multi-dimensional roles in pathogenesis of the virus in the host.

## Tools for defining glycan-specific targets in virus–host interactions

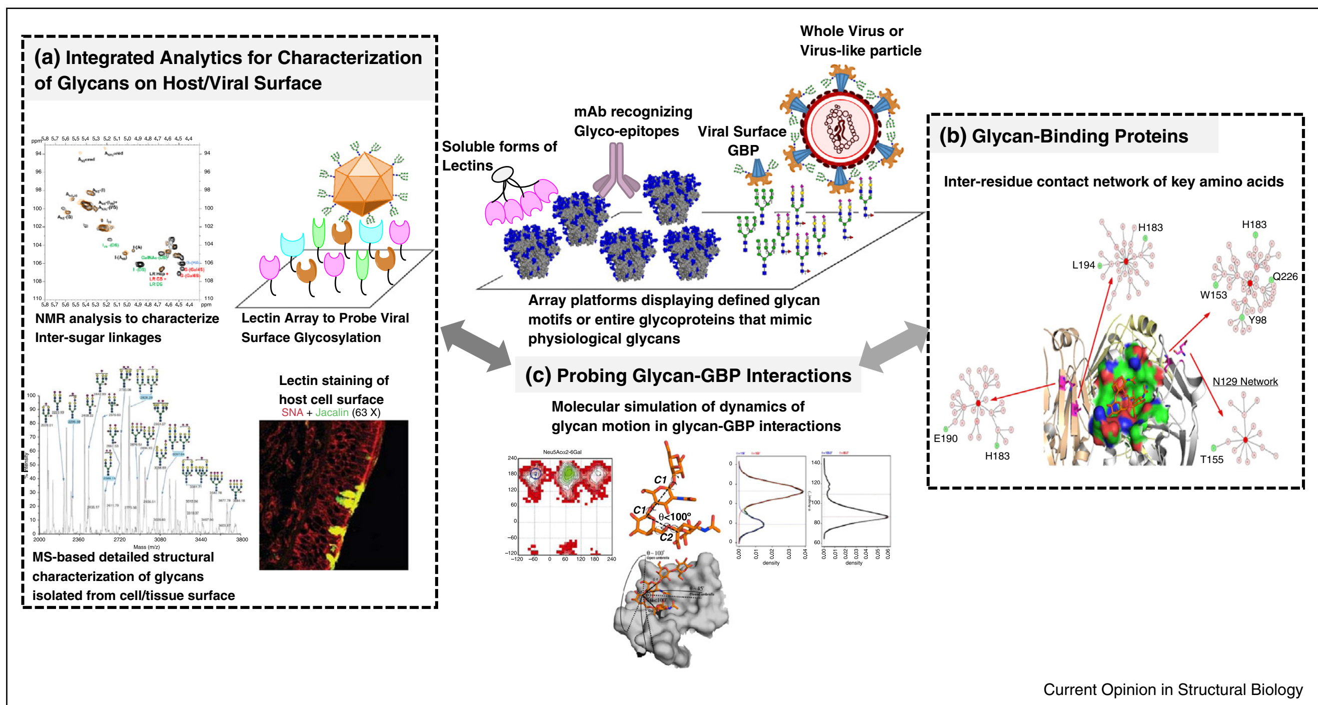
The dynamic interplay between virus and its mammalian host involving glycan–GBP interactions presents new opportunities to target these interactions so as to develop novel antiviral therapies. Based on what is known about role of complex glycans in viral–host interactions, the key question is how does one define a target in the right physiological context of these interactions? [43] Given that glycosylation biosynthesis machinery is complex and does not have a template, the results from *in vitro* experiments may be biased towards glycans made by a given cell line used in the experiment and may not be related to the actual physiological context of the virus–host cell interactions. For example, the glycosylation on gp120 protein on the surface of the virus is different from that of a recombinantly expressed protein in different cell lines [62•,63,64]. Therefore, framing this question would guide the integration of the datasets from the various tools developed to decode glycan structures and glycan–protein interactions. Some of the key tools and perspectives on how to integrate the tools from the standpoint of characterizing glycan–protein interaction targets is summarized in the following (schematic of the integration of tools shown in Figure 2).

### Structural characterization of glycans

The characterization of glycan-specific targets in virus-host interactions can range from simple to very complex definitions. An example of a simple glycan-specific target is a single terminal sugar such as sialic acid as seen in the case of neuraminidase inhibitors or a defined oligosaccharide glycan motif such as tri or tetra-saccharide motif capped by α2-3 or α2-6-linked sialic acid that has specific recognition and high affinity binding by the viral surface glycoproteins. A highly complex description of glycan target would involve defining the glycan motif, the linkage of the glycan comprising this motif to specific glycosylation site on a specific protein and a geometrical arrangement of such glycosylation sites on the glycoprotein. An example of such a complex definition is the glyco-epitope surfaces on HIV gp120 targeted by potent broad spectrum neutralizing antibodies. Therefore the scope of the target definition would guide the development and integration of diverse analytical tools.

The GBPs or lectins that are known to recognize specific glycan motifs are valuable tools that can be used to assess the distribution of these motifs. Furthermore, the advances in chemical synthesis of glycans coupled with the ability to probe finer nuances of glycan motif recognition by various lectins using glycan array platforms has substantially improved the knowledge on the diversity of glycan motifs recognized by various GBPs [65•,66]. These GBPs can be directly used to stain host cell or tissue surfaces and multiplexing the staining of more than one GBP can expand the knowledge of the glycan motifs distributed on these surfaces [4,67,68]. As an example co-staining of host tissues or cells with *Sambucus nigra* agglutinin I (SNA-I) which binds with high specificity to α2-6 sialylated glycans and Concanavalin A (ConA) which binds to trimannosyl core of N-linked glycans would give information on predominance of α2-6 sialylated glycans that are N-linked to the glycoproteins. These lectins can also be displayed in an array-like

Figure 2




Tools to define glycan-specific targets in viral–host interactions. **(a)** Shows snapshots of various analytical tools that either directly probe glycans in the appropriate physiological context (such as lectin-based staining and lectin array) or provide detailed characterization of glycans isolated from host or viral surface (using mass spectrometry and NMR based approaches. **(b)** Shows analysis of GBPs and their glycan-binding site using a network approach which not only takes into account key residues in glycan-binding but also those that are related to these residues through their inter-residue interaction network. **(c)** Shows a schematic of biochemical (top) and structural (bottom) tools to probe glycan–GBP interactions. As shown in the bottom, shape based definitions of the conformational space sampled by glycans relates the conformations defined by 7 different glyosidic torsion angle (for a tetrasaccharide) into a single parameter $\theta$ whose variation can be studied during molecular dynamics simulations.

platform and samples such as whole viruses or virus-like particles comprising of the viral surface glycoprotein can be probed for their binding to such lectin-arrays [65•,69,70,71]. This would again provide information on the prevalence of specific glycan motifs that are present as a part of the glycans on the viral surface glycoproteins. The advantages of using lectins is that it provides a read on the glycan motif in their physiological context either on the host tissue or cell or viral surface and do not require any additional processing that may change the structural diversity of the glycans before analysis. However, a limitation in this approach arises from the lack of a comprehensive panel of lectins that can completely decode the structural diversity of the glycans. As an example while lectins like SNA-I give an accurate picture of distribution of glycans capped by α2-6-linked sialic acid, the information on whether this motif is a part of highly branched N-linked glycans or a part of long oligosaccharide branch length cannot be deduced.

There are several analytical methods building on the use of different mass spectrometric methods such as MALDI-MS, LC–MS, tandem MS–MS, and other methods using NMR spectroscopy, and HPLC that have been developed over several decades for detailed structural characterization of complex glycans, glycopeptides and glycolipids. Each analytical method is unique but they provide overlapping information on the detailed nuances of glycan structure, occupancy of the glycosylation site, etc. Therefore integration of information from different analytical techniques would provide comprehensive information on the glycan structures displayed on host and viral surfaces. One limitation of this approach is the challenges in accessing and isolating glycans from their right physiological context before analysis. For example, the HA from influenza A virus subtypes H1N1 and H3N2 that have adapted well to the human host shows extensive staining of non-ciliated goblet cells in the upper respiratory epithelial surface. However it is challenging to obtain and grow these cells *in vitro* to extract the glycans from these cells for detailed structural analyses.

Therefore, depending on the scope of glycan target definition it would be necessary to employ both lectin-based tools and analytical tools and integrate the information from applying these tools for an unbiased definition of the

target. Such an approach was used to expand the target definition of sialylated glycan receptors for human adapted influenza A viruses going beyond just the terminal α2-6 sialic acid linkage to a long oligosaccharide motif capped by α2-6 sialic acid both in the context of N-linked glycans on the ciliated epithelial surface and non-ciliated goblet cell surface in respiratory tract of humans and established animal models such as ferrets [44,68,72].

## Probing glycan–GBP interactions

A variety of biochemical methods have been used to characterize the specificity in the context of multivalent GBP–glycan interactions. Among the various tools, glycan array platforms are rapidly emerging as a popular tool to probe finer nuances of glycan structures that are recognized by various GBPs. Glycan platforms consist of hundreds of synthetic glycan motifs (typically present on N and O-linked glycoproteins and glycolipids) displayed on the surface of the array. Multiple types of arrays have been developed that utilize different strategies including the formation of neoglycolipids [73], neoglycoproteins [74], or the direct application of glycans to various surfaces [75–80]. Studies have also begun to adapt these technologies towards the presentation of natural glycans by harvesting glycans from the cells or tissues and imprinting these on a glycan array format, thus allowing one to probe the glycan repertoire of a biological system [81].

Designing the experimental method and array platform to probe glycan–GBP interactions needs to be carefully done based on the scope of the analysis. In most cases the scope of the analysis is to obtain a primary screen of a whole virus or viral surface glycoprotein or mammalian GBP against the maximum diversity of glycan motifs that can be generated in a defined fashion synthetically. Following this primary screen, the second objective is to usually probe deeper into the quantitative differences in affinity and avidity between different viruses for specific glycan motifs. This would often involve doing a dose-dependent binding of the viral surface glycoprotein (or whole virus) to defined motifs in secondary assays such as surface plasmon resonance or isothermal titration calorimetry [77,82]. It is important to understand the glycan target motif while designing the glycan arrays for probing nuances of glycan binding specificities. For example, if one were trying to understand the nuances in binding of antibodies that target glycan shield of HIV surface protein gp120-gp41, then using an array of just different high mannose and complex glycans may not fully capture the nuances in the antibody-binding given that the underlying peptide epitope would not be present in such a platform. This might lead to confounding interpretations on link between target glycan motif recognized by these antibodies and their neutralization potential in *in vitro* and *in vivo* assays. It is therefore be more appropriate to use the recently developed BG505 SOSIP.644 gp120-gp41 trimeric unit [83] expressed in different cell types (and also mutant forms that lack specific glycosylation sites) by presenting this trimeric unit and its variants on an platform to probe the nuances of glycan recognition by the glycan shield targeting antibodies.

## Structural and molecular specificity of glycan–GBP interactions

At the three-dimensional structure and molecular level, the interactions between glycans and GBPs have been captured in numerous X-ray co-crystal structures of viral surface glycoprotein–glycan receptor complexes and antibody-glyco-eptiope complexes as in the case of HIV. Over the past several years, there has been a substantial progress in developing tools for accurate molecular simulation of glycan–protein interactions including improvement in force-fields to include glycan-specific parameters [84]. This progress has led to improvements in modeling the electron density of glycans to assign their coordinates in the co-crystal structures and also rectify errors in past assignments pertaining to incomplete ring closures, inaccurate ring and exocyclic torsion angles, etc. [85,86•,87]. The growing wealth of GBP-glycan co-crystal structures and development of molecular simulation tools have permitted successful predictions of amino acid changes that would alter glycan-binding specificity of the GBP. A couple of areas where this approach has been extensively applied is in prediction and validation of mutations in influenza A virus HA that would switch its binding specificity from α2-3 to α2-6 sialylated glycan receptors [4,88–90] and in engineering antibodies that target known glycan epitopes to alter their epitope specificity [91–93].

More recent studies have described glycan-binding sites by mapping the three-dimensional structure into a two-dimensional network of non-bonded inter-residue interactions involving key residues that contact the glycan structure [88,94]. This network approach has permitted obtaining insights into the molecular determinants of glycan receptor-binding specificity of influenza A virus HA going beyond just the residues that contact the glycans. This include role of site-specific glycosylation that impacts receptor-binding specificity [58,59]. This network approach had also provided a framework to investigate amino acid changes required to switch glycan receptor-specificity (from α2-3 to α2-6 sialylated glycan receptors) of the H5N1 influenza HA in the context of additional changes in the glycan-binding site resulting from natural sequence evolution [88]. Importantly the network analyses studies transformed the notion of hallmark residues across different strains associated with glycan-binding specificity by demonstrating that each strain depending on its sequence evolution needed distinct set of amino acid changes to switch receptor specificity.

On the glycan side, the availability of co-crystal structures and molecular simulation tools has provided insights into the preferential conformations of the glycans sampled in

the unbound and protein-bound states. In fact, the conformational space sampled by sialylated glycan receptors in binding site of avian and human influenza HA has been described using shape-based definitions such umbrella and cone-like topologies. These shape-based definition of the glycan conformational space simplifies the parameterization to capture the conformational sample going from a series of glyosidic torsion angles to a one or two parameters that capture the shape [44]. In addition to X-ray co-crystal structures, glycan–GBP complexes have been analyzed in solution using various NMR methods including STD-NMR. For example, NMR analyses of α2-3 and α2-6 sialylated glycan receptors bound to different HAs complimented the information on glycan–protein contacts from the X-ray co-crystal structures by providing additional information on dynamics of glycan motion in the free and protein-bound states [95,96].

Unlike protein–protein interactions that cover a large surface area on both interacting proteins, protein–glycan interactions cover substantially lower surface area on the protein which is consistent with the low to moderate binding affinity of a given glycan-binding site to a given glycan-motif. Despite this affinity, there is specificity in the glycan-binding site — glycan contacts which is also governed by the dynamics of glycan motion in the binding site compared to the unbound state. As a result, mutations in the amino acid that directly contacts the glycan or in other amino acids in its network of inter-residue contacts are likely to significantly impact the glycan-binding properties of the GBP. Thus it is important to capture the network properties on the protein and dynamics of glycan motion while modeling the molecular interactions between glycans and GBPs so as to engineer these interactions in a predictable fashion.

## Summary

Complex glycans play multidimensional roles in various stages of viral pathogenesis in a given host starting from viral attachment and entry to host immune response to counter the infection. The advances in development of tools to chemically synthesize glycans, sophisticated analytical methods for structural characterization of glycans, novel array platforms to simultaneously probe interactions between multitude of GBPs and glycan motifs have transformed our understanding of these multidimensional roles. However, given that the context of glycan–GBP interactions (in different hosts, within the host versus outside the host in *in vitro* assays) critically impacts the structural diversity of the glycans, there are gaps in bridging the definition of glycan-based targets to the biological functions in viral pathogenesis mediated by these interactions. Therefore one has to take an integrated approach by bridging different tools such as synthetic, analytical, array platforms, molecular modeling to fill these gaps and appropriately frame and validate target definition in these interactions. Such an approach would substantially augment ongoing efforts to in targeting glycan-GBP interactions to develop vaccine strategies as in the case of HIV or novel antiviral therapeutics.

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