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Glycan and Its Role in Combating COVID-19

Swapan Kumar Chatterjee and Snigdha Saha

Abstract

Newly identified beta-coronavirus i.e. the 2019 novel coronavirus is associated with a contagious transmittable respiratory disease called COVID-19. This disease has been declared as a “pandemic” by the World Health Organization (WHO). The entry of coronavirus in the human respiratory epithelial cells depends upon the interaction between host cell receptor ACE2 and viral S-glycoprotein. However, this type of molecular recognition in between cell surface receptors and envelope glycoproteins are mediated by specific glycan epitopes and attribute to viral entry through membrane fusion. Glycans are essential biomolecules made by all living organisms, have roles in serving structure, energy storage, and system regulatory purposes. The glycan shield plays a crucial role in concealing the surface S protein from molecular recognition. The immunomodulatory properties of Glycan-binding proteins (GBPs) like Lectins, build them as an attractive candidates for vaccine adjuvant. Investigations involving the complement system activation by the lectin pathway in COVID-19 and diseases are in need of the hour. The innate immune response involving complement system could have varied biological effects against an array of microbial infections. The advances in glycoprotein style methods especially immunomodulatory action of some lectins are necessary to boost the effectiveness of treatment of COVID-19 and other pandemics.

Keywords: Glycan, S-glycoprotein, ACE2 receptor, Glycan binding protein (GBP), COVID-19

1. Introduction

A new virus called the 2019 novel coronavirus (an enveloped beta-coronavirus) is identified in December 2019 and associated with a de novo contagious respiratory disease. The coronavirus disease 2019 (COVID-19) has been declared as a “pandemic” by the World Health Organization (WHO). Previous reports have recognized various human coronaviruses, like in 2003 SARS-CoV, in 2004 HCoVNL63, in 2005 HKU1, in 2012 MERS-CoV, and now in 2019 pathogenic SARS-CoV-2. In humans, the effects of these viruses are correlated with severe respiratory tract infections. COVID-19 disease has signs that are similar to a common cold. However, this infection can lead to serious respiratory failure, as well as compromised and harmful immune responses. Increased monocyte-neutrophil ratios and exacerbated release of inflammatory mediators particularly IL-6, characterize this condition, which can contribute to organ dysfunction. Given the fact that other coronavirus outbreaks have occurred, there is no known treatment or vaccination for COVID-19.

Another major problem is the urgent need for easy and fast instruments to detect viruses in clinical and environmental samples. Early identification of SARS-CoV-2 in asymptomatic and/or presymptomatic individuals is crucial for stopping the transmission chain [1]. Plasmapheresis is also essential for extracorporeal removal of SARS-CoV-2 from blood in order to present alternative therapies. These dynamic pictures have imposed a fight against time through numerous fields of knowledge such as biomedical research, biotechnology, drug production, and molecular analysis in order to find as many resolutions as possible to these and other complications presented by the pandemic.

Viral members of the CoVs family restrain a positive-sense, single-strand RNA genome, which are 26 to 32- kilo bases in length [1]. The infectivity and immeasurable distribution capacity of CoVs have been established them as an important pathogen. In addition to numerous avian hosts, various members of CoVs have been recognized in a range of mammals, like masked palm civets, bats, dogs, mice, camels, and cats are responsible for disease related to gastrointestinal systems, hepatic, respiratory, and nervous system in humans. The outer surface membrane (M), envelope (E), and spike (S) structural proteins are coupled within the envelope of coronavirus which consists of a lipid bilayer. It is believed that glycosylated SARS-CoV-2 spike (S) protein, mediates host cell entry by binding to the angiotensin- converting enzyme 2 (ACE2) and establish the host tropism. Similar to many other viral fusion proteins, the SARS-CoV-2 spikes also utilize a highly dense coating of non-immunogenic or weakly immunogenic complex carbohydrates - glycan shield to thwart the host immune response [2]. Glycans are carbohydrate-based polymers made by all living organisms. The heavily glycosylated SARS-CoV spike protein suppresses almost 23 putative N-glycosylation sites, amidst 12 of them are effectively glycosylated [3]. In viral fusion proteins presence of N-glycan coating is correlated with protein glycosylation and plays a decisive role in viral pathogenesis. The N-glycans expressed on the surface of viral envelope glycoproteins have very diverse biological roles and are all inextricably linked to their nature. However, molecular recognition in between cell surface receptors and envelope glycoproteins are mediated by specific N-glycan epitopes and attribute to viral entry through membrane fusion. Moreover, an extremely dense coating of non-immunogenic or feeble immunogenic complicated carbohydrates on otherwise perilously exposed viral proteins constitutes an ideal camouflage (or shield) to evade the system [4].

The glycan shield plays a crucial role in concealing the surface S protein from molecular recognition. However, to effectively perform, the spike has to acknowledge and bind to ACE2 receptors as the primary infection route. For this reason, the RBM should become absolutely exposed and accessible. During this situation, the glycan shield works as one with an outsized conformational modification that permits the RBD to emerge higher than the N-glycan coverage. Each the S-glycoprotein and ACE2 receptor are proverbial to be extensively glycosylated, i.e. they contain covalently linked complex oligosaccharides referred to as glycans. Recently published studies have shown that the spike glycoprotein contains sixty-six glycosylation sites with forty-four of them being enclosed within the model. Another recent study analyzed site-specific N-linked glycosylation of MERS and respiratory illness SARS S glycoproteins, indicating that every of those glycosylation sites is occupied by up to 10 totally different glycans (called glycoforms), which greatly extends epitope diversity [4, 5].

The synthesis, folding, and glycosylation (as alternative PTMs) of infectious agent proteins depend upon host organelles (ribosome, endoplasmic reticulum, and Golgi apparatus) and enzymes (glycosyltransferases and glycosidases). The present experimental knowledge relating to the glycosylation of viral proteins depends on the carbohydrate processing enzymes present within the

biological systems accustomed to propagate the viral strain. During this sense, our data regarding the natural pattern of viral protein glycosylation is incredibly restricted. It's conjointly vital to think that viral proteins could follow totally different pathways than those discovered from host glycoproteins [5, 6]. Attribute to their chemical complexity and restricted sensitivity of existing analytical instruments, glycans are left neglected. This can be unfortunate as they verify a major part of the structure and performance of the many glycoproteins. This can be very true within the field of host/pathogen interactions, wherever glycan diversity is employed by each host to evade recognition by pathogens and therefore the pathogens to flee the system response. Moreover, glycans, and specifically their outmost components, have vital conformational flexibility. This contributes to the overall conformational dynamics of the molecule that may each generate novel potential drug binding sites or shield binding sites predicted mainly from polypeptide-only models [7].

Beyond a function in shielding the underlying proteins from recognition by antibodies, the glycans on infective proteins may additionally attenuate the flexibility of the host system to lift antibodies against any epitopes that embrace the glycan. In an exceedingly T-cell-dependent adaptative immune reaction, peptides from the infective agent are presented on antigen-presenting cells by major histocompatibility complex II molecules, conjointly referred to as human leukocyte antigen (HLA) complexes. HLA complexes have the most popular peptide antigen motifs, and supported data of those preferences it's doable to predict that peptides in exceedingly infective proteins are probably to be HLA antigens [8]. However, once that peptide contains a glycosylation site, the probability of the peptide to be presented in an HLA complex could also be compromised, if as an example the peptide cannot bind to the HLA molecule owing to the steric presence of the glycan. However, glycopeptides could also be presented in HLA complexes if the glycan is compact enough or if it's found on the end of the peptide antigen wherever it does not interfere with HLA binding. The glycan-mediated shielding of predicted HLA antigens derived from the S glycoprotein is conjointly containing a glycosite. Glycosylation systematically decreases the surface exposure of the residues proximal to the glycosites however conjointly junction rectifier to non-sequential changes in exposure, as a result of the 3D topology of the protein surface within the close proximity of every glycosite [8, 9].

The SARS-CoV-2 envelope glycoproteins are involved in the viral adhesion and entry processes. The presence of glycoproteins in the viral envelope opens up a world of possibilities for using carbohydrate-binding agents like lectins to fix some of the pandemic's most pressing issues. Lectins can recognize glycans, allowing them to be used in a number of biotechnological applications. The presence of glycoproteins on the viral envelope unfolds a large vary of prospects for the application of lectins to deal with some urgent issues concerned during this pandemic. The growing popularity of glycans enables the use of lectins for many biotechnological applications. Significantly, these agglutinins block the viral adhesion to the host cells by targeting the sugar moieties in surface proteins, and are considered as broad-spectrum inhibitors of viral invasion. The interaction with glycoproteins conjointly allows the use of lectins within the development of devices for identification and characterization of glycoproteins in a viral envelope or alterations in host glycoproteins throughout virus infection. Lectins are natural proteins that focus on the sugar moieties of a large vary of glycoproteins [10]. They are prevailing among higher plants and are divided into seven families of structurally and evolutionarily connected proteins. Over a decade ago, studies revealed that through inhibition of virus-cell fusion, plant lectins were reportable to inhibit HIV replication in lymphocyte cell cultures [9].

Sugar-binding proteins that are neither antibodies nor enzymes are known as lectins. To be labeled as a lectin, a glycoprotein must meet three distinct criteria. To begin, lectin is a carbohydrate-binding protein or glycoprotein (s). Second, lectins aren't the same as immunoglobulins (antibodies). Finally, lectins do not alter the biochemistry of the carbohydrates they bind. Plant lectins are a specific type of carbohydrate-binding proteins which are capable of specific recognition and reversible binding to carbohydrates. Since lectins can recognize specific carbohydrate structures such as proteoglycans, glycoproteins, and glycolipids, they can control various cells through glycoconjugates and their physiological and pathological phenomena via host-pathogen interactions and cell-cell communications.

Initially, it had been reported that plant lectins inhibit virus replication by forestalling virus adsorption however studies had been later shown that they prevent the fusion of HIV particles with their target cells. Additionally to the antiviral impact of mannose- and N-acetylglucosamine-specific agglutinins on HIV, the associate repressive impact of those plant lectins was reported on respiratory syncytial viral infection, CMV infection, and influenza A virus infection in vitro. Carbohydrate-binding agents are thought of as anti-CoV agents that focus on spike protein and restrain CoV entry [10]. They're proficient to bind specifically with the oligosaccharides on virus surfaces like HIV and S glycoprotein. In mouse model and additionally, in vitro condition they inhibit a large variety of CoVs, as well as SARS-CoV, HCoV NL63, HCoV 229E, and HCoV OC43. Plant lectins, such as those present in leeks, have been shown to be effective coronavirus inhibitors by interacting with two targets in the viral replication cycle. The first target was discovered early in the replication cycle, most likely during viral attachment, while the second was discovered toward the end of the infectious virus cycle. Depending on the nature of their sugar specificity, the antiviral activity spectrum of plant lectins varies considerably. In general, the plant lectins which were mannose-specific found to be highly effective against coronaviruses. Mannose-binding glycoprotein (MBL; additionally called mannan-binding lectin) could be a pattern-recognition molecule that plays a critical role in spacing and orientation of the carbohydrate-recognition domains [2, 10].

In several expression systems, glycosylation act as a live to gauge antigen quality. For styling appropriate immunogens for vaccine development, it is important to have basic understanding concomitant with the RBD domain of the SARS-CoV-2 spike protein which is able to incorporate complicated sialylated N-glycans and

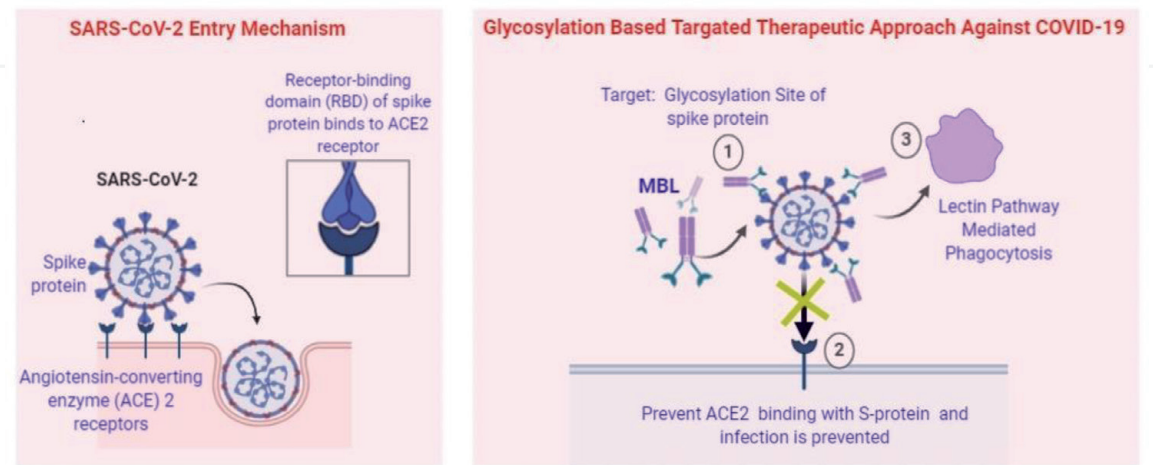


Figure 1. Potential role of MBL in prevention of SARS-CoV2. 1. Attachment of MBL at the glycosylation site of spike protein by “Lock and Key” mode. 2. Prevent ACE2 mediated entry of viral pathogen. 3. Lectin pathway-mediated phagocytosis of intracellular pathogens (adapted from reference [2]).

sialylated glycoprotein O-glycans. The interaction with glycoproteins additionally permits the utilization of lectins within the development of devices for the identification and characterization of glycoproteins in infectious agent envelopes or alterations in host glycoproteins throughout virus infection. MBL could be a serum C-type glycoprotein, that is in a position to bind SARS-CoV intrinsically or infected cell and additionally capable to inhibit the infectivity of the virus. Hence, with this background knowledge, we could to anticipate that glycosylation of infectious agent peptides by “Lock and Key Technology” may be considerate as a novel therapeutic strategy against the current COVID-19 pandemic (**Figure 1**) [2, 10, 11].

2. Glycosylation and its role in onset of disease

The “glycome biology” or “glycobiology” studies the thorough repertoire i.e. the structure, biosynthesis, and biology of glycoconjugates composed of carbohydrate chains, or glycans, which are covalently, linked to lipid or protein molecules. The formation of glycoconjugates, differences in their glycan sequences, their length, and the connection between them depends upon on a process called glycosylation. Synthesis of glycoconjugate is a dynamic process that relies on the sugar precursors, the local milieu of enzymes, structures of organelle as well as cellular signals, and the cell types. Studies of rare genetic disorders that have an effect on glycosylation 1st highlighted the biological importance of the glycome, and technological advances have improved our understanding of its heterogeneousness and quality. However the replication process of secreted and cell-surface glycomes, overall cellular standing in health and sickness requires a detail research and assessment. In fact, changes in glycosylation will modulate inflammatory responses, alter viral immune escape, promote neoplastic cell metastasis, or regulate apoptosis; the composition of the glycome conjointly affects urinary organ operate in health and sickness. Easy and extremely dynamic protein-bound glycans also are well endowed within the nucleus and living substance of cells, wherever they exert restrictive effects. In fact, additionally to forming vital structural options, the sugar elements of glycoconjugates modulate or mediate a good form of functions in physiological and pathophysiological states. Glycoproteins and polysaccharides have vital functions in viral cells, and even glycoproteins have central roles within the biology of most viruses [10, 12]. Glycoconjugates are measured by the addition of sugars to proteins and lipids. A huge range of naturally occurring sugars will be combined to make a variety of distinctive glycan structures on lipid and protein molecules that modulate their activity. Multiple enzymatic site preferences, similarly because the use of stereochemical α or β conjugations, produce diversity in wherever and the way these sugars are linked to every alternative. In fact, altogether, these options imply the potential existence of ~10¹² completely different branched glycan structures.

Protein glycosylation includes the addition of N-linked glycans, O-linked glycans, phosphorylated glycans, glycosaminoglycans, and glycosylphosphatidylinositol (GPI) anchors to amide backbones similarly to C-mannosylation of essential amino acid residues. Glycolipids are glycoconjugate which include glycosphingolipids (GSLs) formed through the addition of sugars to lipids. Glycosylation of proteins and lipids happens within the endoplasmic reticulum (ER) and with most of the terminal processing occurring within the cis-, medial- and trans-Golgi compartments. In these organelles, glycosidases, and glycosyltransferases form carbohydrate structures in a series of steps that are dominance by the availability of the enzyme activity, substrate, levels of gene transcription, and enzyme location. In fact, the glycome of a specific cell reflects its distinctive gene-expression pattern that controls the level of the enzymes responsible for glycoconjugation.

The glycome is created in a non-templated manner and is in an elaborate way controlled at multiple levels within the ER and cyst, unlike exome or proteome [12, 13].

3. Different type of glycosylation in human

3.1 N-linked glycosylation

The covalently N-linked glycans are superimposed co-translationally to native polypeptides within the endoplasmic reticulum (ER) as blocks of fourteen sugars (Glc3Man9GlcNAc2). These glycans are measure then subject to extensive modification throughout their transport through the ER and also the Golgi body before reaching their final destinations within or outside the cell. Within the ER and also the early secretory pathway, the sugar repertoire is still very little. Within the Golgi body, however, the glycans acquire complicated and extremely numerous structures by terminal glycosylation, which ends up in a very tremendous heterogeneity. Such diversity differs between cell sorts, tissues and species, and helps to additional increase micro-heterogeneity in the presence of the same genetic polypeptide background. This leads to the creation of new functionalities and specificities. The N-glycans may also have a very important role in correct macromolecule folding and degradation, and solubility, by avoiding the precipitation that's caused by lipophylic aminoacid stretches within the emergent polypeptide. The presence of a glycan protect on the peptides additionally allows the protection of the glycoproteins against degradation by proteases [13, 14].

3.2 O-linked glycosylation

Glycosylation will occur on amino acids with functional hydroxyl group teams, that is most frequently Ser and Thr. In humans, the foremost common sugars joined to Ser or Thr are GlcNAc and N-acetylgalactosamine (GalNAc)7. GalNAc-linked glycans usually referred to as mucin-type O-glycans, are abundant on various living things and secreted glycoproteins together with mucins, which type an important interface between animal tissue cells and the external tissue layer surfaces of the body. Mucins are characterized by a variable range of tandem repeats with Ser and Thr that create many sites for O-glycosylation. O-glycosylation performs various functions, such as providing resistance to proteolysis of stem regions of membrane proteins, creating specific recognition phenomena, and selection of ligands for selectins. Masking of immunogenic epitopes on the protein is in need to special mention [13, 14].

3.3 Glycosphingolipids

GSLs comprise a sphingolipid to which a glycan is connected at the C1 group position of a ceramide; they are one in every of the foremost plentiful glycolipids in humans are generally found within the lipid bilayers of cellular membranes. GSL glycosylation starts with the addition of glucose or galactose to the lipid moiety at the protoplasm facet of the ER or the Golgi body; however, the structure is then flipped to the luminal side for the additional process. The enzymes that initiate GSL glycosylation are specific for lipids, but an additional process of the sugar chain is performed by additional general glycosyltransferase [13, 14].

3.4 Proteoglycans and glycosaminoglycans

Proteoglycans are glycoproteins within the extracellular matrix that, in addition to containing canonical N-glycans and O-glycans, are characterized by the presence

of long sugar repeats connected via O-linked glycosylation motifs [13, 14]. These extended sugar chains are termed glycosaminoglycans and contribute to a considerable proportion of the proteoglycan's molecular mass. Whereas N-glycans generally embrace 5–12 monosaccharides, a glycosaminoglycan motif will simply contain more than eighty sugars (for example, keratan salt is a poly-N-acetyl lactosamine chain that contains up to fifty oligosaccharide units). These long chains are constructed through oligosaccharide repeats fashioned by GlcNAc or GalNAc, combined with associate uronic acid (that is, glucuronic or iduronic acid) or brain sugar. Glycosaminoglycans are functionally various and include heparan salt, chondroitin salt, keratin sulfate, and hyaluronan. Glycosaminoglycans are crucial to the formation of the glycocalyx, an important structure for the upkeep of the cytomembrane that conjointly functions as a reservoir for sequestered growth factors [13–15].

3.5 Role of glycans in immunity and inflammation

Cells of the immune system, equally to any or all different cells, express cell surface-associated glycoproteins and glycolipids that, besides glycan-binding proteins and different molecules, sense environmental signals. Many immune receptors that are expressed on innate and adaptive immune cells acknowledge glycans found on the surface of microorganisms that are referred to as pathogen-associated molecular patterns. Examples of such glycan-containing molecules embrace bacterial lipopolysaccharides, peptidoglycans, teichoic acids, capsular polysaccharides, and fungal mannans. The recognition of those glycosylated microbial patterns by the immune system has been exploited for the vaccine's development, example diplococcus vaccines, are developed employing a mixture of capsular polysaccharides. The recent progress in HIV-1 immunogen development has conjointly been driven by a far better understanding of the HIV-1 envelope (Env) conjugated protein and the effects of its glycan composition on immune responses and immune evasion [15, 16].

Pro-inflammatory cytokines may contribute to inflammatory vascular diseases by inducing changes in cell-surface N-glycosylation of epithelial tissue cells. In the adaptive immune system, glycans even have crucial and multifarious roles in B lymphocyte and lymphocyte differentiation. These functions involve multiple cell-surface and secreted proteins (such as CD43, CD45, selectins, galectins, and siglecs), differing kinds of cell–cell interactions, and also the recognition of glycan-containing antigens. The regulation of cellular glycosylation and its impact on the molecules that perform as ligands and receptors throughout associate inflammatory response is controlled through numerous mechanisms and is dependent on the inflammatory insult. These mechanisms, that embrace ERK, and p65 signaling are vital to understanding the failure to regulate chronic inflammation in multiple disease states. Immunoglobulins, for instance, are crucial parts of humoral immunity, and altered glycosylation patterns of some antibody isotypes are known in chronic inflammatory reaction, and infectious diseases, like arthritis (RA), systemic lupus erythematosus (SLE), and HIV infection [16, 17].

The glycoproteins CD43 and CD45 are profusely expressed on the surface of B cells and T cells and contain each O-glycans and N-glycans. Glycosylation of those proteins is modulated throughout cellular differentiation and activation and regulates multiple T cell functions, as well as cellular migration, T cell receptor signaling, cell survival, and apoptosis. CD45 has an active receptor-like protein tyrosine phosphatase domain that interacts with Src family kinases in B cells and T cells to control the signaling threshold for the activation of B lymphocyte receptors (BCRs) and T cell receptors. CD45 additionally has non-catalytic functions, for instance, in modulating the function of the repressive co-receptor CD22 on B cells [17, 18].

Siglecs are sialic acid-binding proteins expressed on several cells of the system that perform varied functions, as well as the regulation of antigen-specific immune responses and cell homing. CD22 is one in all sixteen siglec proteins characterized in humans and is expressed on B cells, wherever it specifically binds α -2, 6-linked sialic acid-containing ligands; this interaction is crucial for the formation of nanoclusters within the cell wall that manage BCR signaling following antigen binding [17, 18].

The selectin family of proteins consists of E-selectin, P-selectin, and L-selectin that are chiefly expressed on epithelium cells, platelets, and leukocytes, respectively. These cell adhesion molecules are vital for white cells rolling on the epithelial tissue before tissue extravasations. Another study demonstrates that targeting selectins could be helpful in some inflammatory diseases. Immunoglobulin isotypes disagree within the variety of N-glycans present on their serious chains. Some immunoglobulin, such as IgA1 and immune globulin, additionally contain O-glycans, which are sometimes clustered within the hinge-region segments of these antibodies. Immunoglobulin glycans impact the effect or functions of antibodies counting on the branching of N-glycans and/or the terminal sugars of N-glycans or O-glycans that embody brain sugar and sialic acid. In fact, immunoglobulin glycosylation can verify glycoform is pro-inflammatory, like Ig with galactose-deficient N-glycans, or anti-inflammatory drug, like Ig with sialylated N-glycans [17–19].

3.6 Glycan and COVID-19

Coronavirus illness 2019 (Covid-19) has a broad clinical spectrum, not nevertheless absolutely delineate or understood, with a regarding the potential for severe respiratory illness, multiorgan involvement, and death. As a result of containment of the virus has verified to be very troublesome, mitigation efforts like mask-wearing, physical distancing, confinement, and quarantines are enforced worldwide leading to restricted exposures/contagious events with also a robust social, health, and economic burden [2]. Since ideal preventive ways like repurposing of known medication to treat Covid-19, and vaccines associated with inevitably long testing, development, and producing time emerges as an attractive approach to timely fulfill the continued need.

Glycoproteins of SARS-CoV-2 are concerned with cell adhesion and invasion, maturation, and modulation response processes. Though alternative SARS-CoV-2 proteins have foreseeable glycosylation sites (such as M-protein, E-protein), the bulk of experimental knowledge is presently accessible on the S-protein. This might be a trimeric protein that mediates viral adhesion through binding to the human angiotensin-converting accelerator two (hACE2) and conjointly interacts with the host immune defense [19, 20].

The S-protein from SARS-CoV-2 has 2 practical subunits (S1 and S2) with 23 potential sites for N-glycosylation and O-glycosylation. Some variations within the glycosylation sites repertoire and famed epitopes are rumored for the SARS-CoV-2 spike protein, despite it's similarity with the SARS-CoV spike (approximately 87.2%). The oligo mannose-type glycans were predominant in 2 sites (N234 and N709). Complex-type glycans were preponderantly exhibited in fourteen organic compound residues (N17, N74, N149, N165, N282, N331, N343, N616, N657, N1098, N1134, N1158, N1173, and N1194), whereas six sites showed a combination of oligomannose- and complex-type glycans (N1074, N801, N717, N603, N122, and N61). The foremost common configuration of oligomannose-type glycans was Man5GlcNAc2. Afucosylated and fucosylated hybrid-type glycans were detected in a minimum of 9 sites. Studies highlighted that the glycosylation profile of the

SARS-CoV-2 S-protein was completely different from those discovered for host glycoproteins or for alternative engulfed viruses. Another experimental study revealed the configuration of the N-glycosylation and O-glycosylation of spike protein subunits, even in the HEK293-based expression system. The authors have solved the structures of N-linked glycans in seventeen foretold sites and rumored the presence of three categories of N-glycans. Significantly, this study discovered O-glycosylation modifications on 2 residues (Thr323 and Ser325) present within the receptor-binding domain (RBD) of the S1 monetary unit. Recently, the characterization of the glycosylation profile of the S-protein expressed in BTI-Tn-5B1-4 insect cells was rumored to show the presence of high-mannose N-glycans altogether twenty two foretold sites. Apparently, these glycans cowl most of the RBD space [17, 20].

The glycan shield plays a vital role in hiding the S protein surface from molecular recognition. However, to effectively operate, the spike has to recognize and bind to ACE2 receptors as the primary host cell infection route. For this reason, the RBM should become totally exposed and accessible. During this state of affairs, the glycan shield works in concert with an oversized conformational amendment that permits the RBD to emerge on top of the N-glycan coverage. The glycans protect the RBD region that does not directly act with ACE2 by “up” and “down” conformations. Ultimately, this analysis shows that the RBM is often accessible once RBD is “up”, whereas it’s terribly well camouflaged when “down”. This implies that the glycan shield of this vital domain is effectively paired with its “down-to-up” conformational amendment, allowing the RBM to transiently emerge from the glycan shield and bind to ACE2 receptors [16, 19, 20].

Protein glycosylation plays a crucial role in the infective agent pathological process, as incontestable by the characteristically thick N-glycan coating of the infective agent fusion proteins. Within the HIV-1 envelope spike (Env), as an example, the protein-accessible expanse is nearly entirely coated in N-glycans. These are thus densely packed that they account for quite half the protein’s mass. The N-glycans present on the surface of viral envelope glycoproteins show terribly diverse type of biological roles. Infective agent entry through membrane fusion is initiated by envelope glycoproteins through molecular recognition events involving cell surface receptors, which are usually mediated by specific N-glycan epitopes. Furthermore, an extremely dense coating of nonimmunogenic or frail immunogenic advanced carbohydrates on otherwise perilously exposed infective agent proteins constitutes a perfect camouflage (or shield) to evade the immune system. To the current study, the HIV-1 Env glycan defends, which is essentially structured by oligomannose (Man5–9) N-glycans, has been shown to be quite effective in allowing the virus to thwart the system [16, 17, 19].

4. Therapeutic approach of glycomedicine

Developments within the field of glycobiology have enabled the development of a range of glycan-based medical specialties. As an example, envelope conjugated protein gp120 is expressed on the surface of HIV-1, and its variable glycosylation facilitates viral escape from immune detection. Adding new glycan-dependent epitopes to the recombinant gp120 used for vaccination inflated the ability of broadly speaking neutralizing being antibodies to recognize HIV-1, suggesting that this approach is used to optimize vaccination protocols and antigens. Moreover, HIV-1 envelope glycoproteins not solely differentiate HIV-1 clad however can even be wont to estimate the efficacy of vaccine regimens on the premise of protein binding to a panel of gp120 glycan-dependent epitopes 240. As printed antecedently,

glycosylation plays an important role in regulating purposeful immune responses through complex receptor–glycan motif interactions. This site is currently being exploited in Ig therapies [20].

4.1 Role of lectins in COVID 19 and activation of complement pathway

Lectins, are glycan-binding proteins (GBPs) that are present in plants and lots of alternative species, are known to act with various glycan molecules either attached or released to a peptide backbone. This distinctive property has been explored within the development of analytics for glycan determination. Many relevant platforms are according to which lectin-based microarray has incontestable a utility in capturing glycan profiles of therapeutic compound glycoprotein [21].

As antecedently mentioned, the S-protein of SARS-CoV-2 encompasses a crucial role in infectious agent adhesion by binding to hACE2. Therefore, the disruption of this interaction is taken into account as a gorgeous target for antiviral medical care. Some non-mammalian-derived lectins (from plants and bacteria) are pointed as various antiviral agents against swallowed viruses thanks to their ability to acknowledge the glycans present within the structural proteins and to impair the initial steps of the infectious agent pathological process. Given the recent emergence of SARS-CoV-2, solely the glycoprotein isolated from Indian bean [Flt3 receptor-interacting glycoprotein (FRIL)] has been according up to now as an antiviral against this virus. FRIL may be a glucose/mannose glycoprotein conjointly called DLL-I. This protein molecule utterly inhibited the cytopathic result of SARS-CoV-2 (strain hCoV-19/Taiwan/NTU04/2020) toward Vero cells at higher concentrations [17, 21].

According to a study, evaluation of the in vitro antiviral activity of thirty three plant lectins toward coronaviruses (SARS-CoV and feline infectious redness virus). Mannose-binding agglutinins showed the best anti-SARS-CoV effects. Among the studied lectins, the upper selective indexes (SIs) were found for those isolated from alliaceous plant (APA; SI > 222.2), black mulberry (Morniga M II; SI > 62.5), and helleborine (EHA; SI > 55.5). Nettle (UDA) and common tobacco agglutinins (NICTABA), each specific for GlcNAc, conjointly showed promising activity. NICTABA and FTO have conjointly shown restrictive activity against different swallowed viruses as well as respiratory disease A/B, breakbone fever virus kind a pair of (DENV-2), herpes simplex virus varieties one and a pair of (HSV-1 and HSV-2) and human immunological disorder viruses (HIV-1/2). Other plant lectins are shown to exhibit restrictive action toward different coronaviruses. Some mannose-binding lectins: concanavalin A (Con A), amaryllis hybrid antibody (HHA), *Galanthus nivalis* antibody (GNA or GNL) one in every of these studies highlighted the importance of glycosylation within the sensibility of 2 kinds of coronaviruses (mouse liver disease virus and feline infectious redness virus) (**Figure 2**) [17, 21].

Non-plant-derived agglutinins also are pointed as promising agents against coronaviruses, e.g. the mannose-binding-lectins cyanovirin-N (from *Cyanobacterium protoctiste*) ellipsosporum and griffithsin (GRFT) (from red marine alga *Griffithsia* sp.) However, solely GRFT has been evaluated against SARS-CoV and MERS-CoV. This protein molecule binds to multiple sites of SARS-CoV and MERS-Cov glycoproteins with high affinity and inhibits infectious agent entry. In addition, this glycoprotein conjointly reduced the mortality and therefore the severity of fatal pneumonic infection iatrogenic by SARS-CoV in mice. This result is related to the decrease of pro-inflammatory cytokines in infected respiratory organ tissue [17–19, 21].

The mitogenicity and pro-inflammatory properties of lectins raise many queries relating to their worth to treat clinical conditions with severe inflammatory

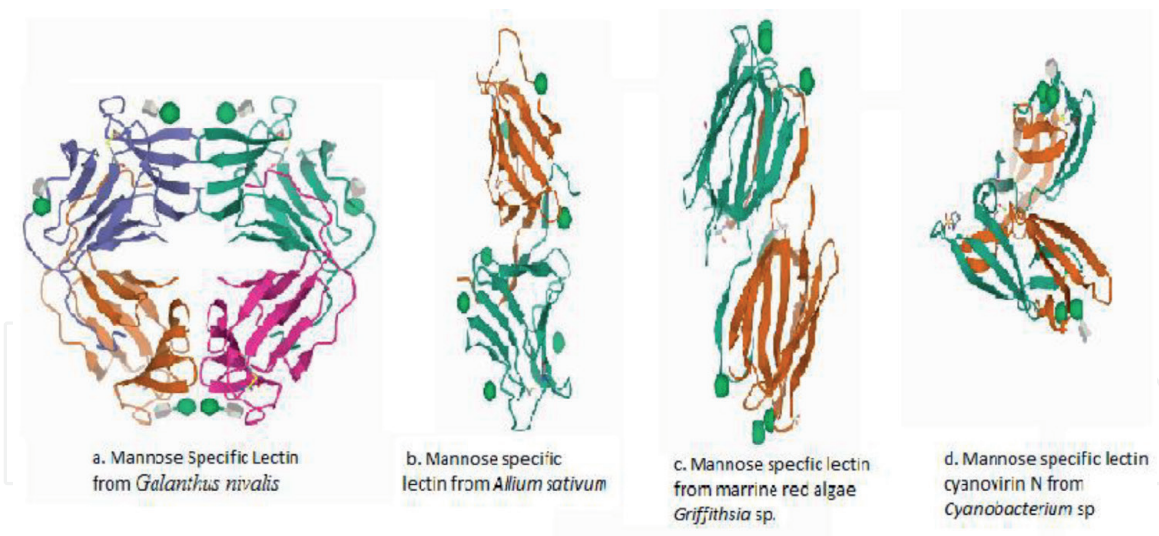


Figure 2.
 Crystal structure of different mannose specific lectins (structures adapted from RCSB PDB).

elements, as seen in COVID-19. The broad-spectrum activity of those agents and therefore the techniques utilized in their style ought to be thought of within the hunt for anti-infective compounds toward SARS-CoV-2. These compounds ought to enhance the response iatrogenic by the immunogen, whereas keeping the equilibrium between body substance and cellular immune responses. Noteworthy to say that even the right induction of Th1-biased response, which is very important for defense against infectious agents, still remains a limitation for a few adjuvants.

Lectins are well-known to push the proliferation of lymphocytes and modulate the discharge of effectors molecules (cytokines and gas oxide) by immune cells. For example, many lectins are potent inducers of IL-12 and IFN- γ production that are key cytokines in the establishment of the Th1 axis. Some lectins may also bind to toll-like receptors and/or increase their expression levels, which can conjointly modulate the discharge of pro-inflammatory cytokines and increase the receptor's ability to acknowledge the pathogens. In fact, the improvement of Th1-based response is very important for protecting immunity against viruses and different intracellular pathogens thanks to the activation of cytotoxic cells (natural killer cells and TCD8 lymphocytes) and production of neutralizing antibodies concerned in immunologic memory. During this sense, the immunomodulatory properties of lectins build them attractive candidates for vaccine adjuvant. Some studies involving glycoprotein as an adjuvant for respiratory disease vaccines need special mention [21].

Innate immunity plays an essential role against numerous pathogens, in that, physical barriers complement components, coagulation cascade, antigen-presenting cells, and immunoglobulins synergistically regulate opsonisation, inflammation, and phagocytosis. Although the innate system might not determine each antigen getting into the host, it will acknowledge numerous microorganisms mainly based on pathogen-associated molecular patterns (PAMPs) present on the cell surface. The notable examples of PAMPs are bacterial peptidoglycan, lipopolysaccharides, mannans, lipoteichoic acids, bacterial DNA, double-stranded ribonucleic acid, glucans, and infective agent surface macromolecule. Duly, the complement system could be a wing of an innate immune response having varied biological effects against a good vary of bacteria, fungal, and infective agent infections [22].

The complement cascade consists of soluble factors and cell surface receptors which will sensitize and counteract against both invading and self-antigens. The complement system bridges the innate and accommodative reaction through

humoral immunity, and by modulating T- and B-cell functions. Complement pathways, which, once activated, lead to consecutive protein reactions, breakdown of complement components C3 and C5, and end in by-products formation (C3a and C5a). These anaphylatoxins elicit an excessiveness of physiochemical responses that successively activate phagocytic cells, and release cytokines, chemokines, reactive element species (ROS), adhesion molecules, and inflammation at the site of infection. Immunoglobulin and cytokines are essential parts of antiviral immunity. In fact, there are 3 main phases of complement activation - (1) foreign molecule recognition, (2) convertase enzyme formation which will cleave C3 and C5, and (3) fabrication of MAC for cell lysis. The alternative, classical, and mannose-binding lectin (MBL) pathways are activation cascades of assorted host-pathogen interaction conditions, joining at the juncture C3, from wherever the central complement cascade proceeds. Among the 3 pathways of complement activation, the MBL pathway is primary in infective agent infections to induce a pro-inflammatory response. Detail Investigations involving the complement system activation by the lectin pathway in COVID-19 and diseases are in need of the hour [22, 23].

5. Conclusion

Glycosylation could be a common modification of proteins and lipids that involves non-template dynamic and complex processes. Glycans have multiple crucial roles in cellular responses to environmental stimuli likewise as cellular growth and differentiation; specific changes in glycan composition are directly joined to several diseases. Technological advances are commencing to overcome many of the challenges display by the complexities of glycoconjugates, improving our understanding of the physiological and pathological processes that are regulated by glycans.

The application of lectins to unravel differing types of issues involved in viral infections like COVID-19 depends upon the presence of glycoproteins within the viral envelope. Within the therapeutic space, the lectins can be thought-about leading molecules for the event of the latest antiviral approaches because of their ability to inhibit microorganism entry within the host cell. The advances in glycoprotein style methods are necessary to spice up the clinical application of those agents thought-about for the treatment of SARS-CoV-2 and alternative microorganism infections. The immunomodulatory action of some lectins may also be exploited to boost the effectiveness of immunization schemes for microorganism infections.

On the opposite hand, lectin-carbohydrates interactions will be accustomed style devices for diagnosing targeting microorganism glycoproteins or host glycoproteins alterations throughout microorganism infections. This kind of apparatuses hold the promise of producing sensitive, quick, and cost-effective identification of infected people and are of important would like throughout the pandemic things, as obligatory for COVID-19.


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Author details

Swapan Kumar Chatterjee* and Snigdha Saha
Molecular Pharma Pvt. Ltd., Kolkata, West Bengal, India

*Address all correspondence to: swapan1chatterjee@gmail.com

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