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Research Article

GLYCOSYLATION OF SARS-COV-2 AND INTERACTIONS WITH IMMUNE SYSTEM

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Abstract

The COVID-19 infection is caused by Betacoronavirus named SARS-CoV-2 (Severe-Acute Respiratory Syndrome Coronavirus-2), which was originated in China in 2019 and spread, all over the world. In the case of SARS-CoV-2, the binding of the angiotensin-converting enzyme 2 (ACE2) receptor and the spike proteins of the virus leads the viral internalization, which initiates the innate immune response. The infection starts with different types of interactions of virus with host cells, and these interactions can be modulated against the infection of SARS-CoV-2 by blocking the ability of ACE2 host receptor to avoid the spreading of disease. The glycosylation of spike protein can be modulated to alter the affinity of ACE2 receptor to affect the infectivity of virus. In this review, we have summarized the mechanisms of spike protein-host cell interactions during infection to develop the immune response and how the modulation of these interactions can help develop vaccines.

Keywords: SARS-CoV-2, ACE2, Glycosylation, Interactions, Immune response

INTRODUCTION

The COVID-19 infection is caused by Betacoronavirus named SARS-CoV-2 (Severe-acute respiratory syndrome coronavirus-2), which has crucial features like high transmission rate, frightening humanity. It was originated in China in 2019 and spread all over the world [1]. Literature have shown that this virus possess around 79% same sequence of nucleotide as possessed by SARS-CoV, which generated the main epidemic situation in 26 countries during 2002–2003[2]. MERS disease (Middle east-respiratory-syndrome) was also caused by the coronavirus called MERS-CoV. Loss of appetite, fever, dyspnea, dry cough, fatigue, gustatory dysfunctions, and olfactory are common symptoms of a COVID-19 patient and decrease in immune cells like helper T cells, cytotoxic T cells, natural killer cells, macrophages, and increased concentration of pro inflammatory cytokines are major conditions of the immune system. COVID-19 infection severity is variable from mild to severe infection of acute respiratory system [3]. The genome of SARS-CoV and SARS-CoV-2 is around 80% identical; the same angiotensin converting enzyme-2 (ACE2) is the cellular receptor for both types of virus and the particles of SARS-CoV-2 are also spherical with spike proteins on the surface like other types of coronaviruses [4]. The size of enveloped SARS-CoV-2 ranges from 65-125 nm and its phylogenetic study revealed that it is a beta coronavirus like SARS-CoV and MERS-CoV. The spike glycoprotein of SARS-CoV-2 is responsible for its adherence and internalization in the host cell, which is a trimer trans-membrane of type I containing 1255 amino acids and it have 22 N-linked glycosylation sequins[5]. The PLpro, RdRp, and 3CLpro are three non-structural proteins, and the spike (S) protein is the structural protein responsible for the host cell recognition, transcription, and replication of SARS-CoV-2. The S protein is a single viral protein responsible for viral entry into cells [6]. The genome of SARS-CoV and SARS-CoV-2 is around 80% identical; the same angiotensin-converting enzyme-2 (ACE2) is the cellular receptor for both types of virus, and the particles of SARS-CoV-2 are also spherical with spike proteins on the surface like other types of coronaviruses [4]. This disease (COVID-19) has a more severe course of action in which the immune system has a weak immune response. The diet of a person significantly affects the gut's microbial composition, which has a crucial role in immunity and inflammatory response. Carbohydrates play significant actions in the metabolism of the body with anti-carcinogenic, anti-inflammatory, cell proliferation, and immune modulatory effects, and the fermentation of carbohydrates in colon generates short chain fatty acids. Selecting the specific carbohydrate and increased dietary fiber intake can help the treatment of COVID-19 patients [7]. The ACE2 receptor and SARS-CoV-2 binding leads the RNA genome release in the cytoplasm. The TLR-3 receptor initiates an immune response to dsRNA during the replication ofSARS-CoV-2 and cascades of signaling process are activated to produce proinflammatory cytokines and type I IFNs. The type I IFN expression is crucial to enhance the generation of antiviral proteins for the protection of other cells. The excessive number of SARS-CoV-2 proteins can interact with TLR-3 signaling to escape the immune response. Virus–host cell interactions help the immune mediator's production in high amount and large quantities of chemokines and cytokines are secreted in the infected cells to response the infection caused by SARS-CoV-2.

Spike Glycoprotein-ACE2 Interactions

Normally Diseases start from the lectin and carbohydrates interactions, so they can be avoided by disrupting these interactions. Vaccination can be done by avoiding the enzymes generating disease-oriented carbohydrates or replacing these enzymes and by using these interactions of lectin-carbohydrates to deliver the drug in the body. Protein epitopes on bacteria have a higher and specific binding tendency for carbohydrates moiety present on the surface of cell for infection pathway to begun. Moreover, some enzymes from bacteria can alter the carbohydrate sequence to increase the surface density of protein receptors, resulting in bacterium's virulence enhancement such as *pseudomonas aeruginosa*

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generates the neuraminidase in patient's lungs to cleave the sialic acid of glycolipid generating the carbohydrate receptor for pathogen adhesion to cell [8]. In COVID-19, trimeric spike glycoprotein of virus causes its penetration in the cell by attaching to angiotensin-converting enzyme receptor (ACE2). Vaccines are developed by neutralizing the antibody production for receptor binding domains (RBD), generally spike proteins are engineered to stabilize the antigen that neutralizes the antibody. Moreover, mRNA based vaccination technique was first identified in 1990, but because of the rapid degradation of RNA in the body, it was developed in the last decade by nanoencapsulation in cationic lipid-based nanoparticles, which provide protection against gastric conditions, for example, vaccines developed for SARS-CoV2 such as Moderna and Pfizer [9]. Glycosylation of the glycans from spikes has great importance in understanding the infection mechanism and the development of a vaccine to eradicate the SARS-CoV2 pandemic. Since the glycans are the main characters for receptor binding, some of the coronavirus (for example, β1-Covs) utilize the glycan-based receptor to carry the 9-O-acetylated sialic acid to bind the spike proteins[10]. The binding of sialic acid promotes the infection and encourages the intercellular expansion of viral infection[11]. The mucous membrane from gastrointestinal and respiratory tracts is affected due to COVID-19, the adjunctive remedies depending on gut microbiota modulation and re-creation of eubiosis may be important approaches for control the harmful effects of COVID-19 [12].

The binding ability of SARS-CoV-2 Spike glycoprotein to ACE2 is 10-20 times higher than in the case of SARS-CoV-1. The glycans are essential for viruses and host cell interactions, viral entry, cleavage of viral protein, and neutralization of viruses by the immune system. The virus-cell adherence may have different mechanisms, such as protein-protein interactions, and the interaction between complex glycan surface and lectins plays an essential role in infection. Numerous interactions involve attachment to sialic acid, which contribute to the complexity and composition variation of glycan chan. The spike protein recognizes the specific sialic acid receptor; for example, in the case of influenza, the upper respiratory epithelial presents Sialylated glycan receptor, including a2,6-linked sialic acid, which is recognized by hemagglutinin [5]. The spike protein of coronavirus specifically recognizes cell surface glycoprotein receptors, and that limits the virus internalization into the cell. The receptor-binding specificity determines the transmissibility of the virus as glycans are distributed in the host. The eight sites of spike glycoprotein have oligomannose-type glycans, which are essential for protein folding and host proteases priming, and the remaining 14 sites are glycosylated through the complex glycan type. In the spike protein and ACE2 receptor, the heterogeneity of several glycosylation sites can be modulated by many glycan structures, producing diversity in the site-specificity-oriented glycosylation. The SARS-CoV-2 spike glycoprotein epitopes are highly fucosylated, 98% of the glycans contain fucose residues, and in the S1glycoprotein, the O-type glycosylation may be involved in the stability and functions of protein [13, 14]. The modulation of viral spike glycoprotein by its glycosylation may be helpful in vaccine development strategies. On the human receptor ACE2, the glutamine 394 in the CoV-2 RBD is identical to residue 479 of CoV-1, which indicates a high affinity of CoV-2 spike glycoprotein for human ACE2 receptor and high efficacy to spread. The glycan–glycan interactions between S glycoprotein and ACE2 interpret the diversity of glycosylation which is responsible for the infection. Moreover, it is important to investigate the glycosylation diversity between the interactions of spike protein and ACE2 receptor to evaluate its effect on immunological responses and antibodies neutralization [15, 16].

SARS-CoV-2 Infection and Immune Responses

In SARS-CoV-2 infection, the viral entrance initiates the innate immune responses, which triggers the inflammatory mechanisms. The binding of ACE2 to SARS-CoV-2 spike protein lead the release of RNA genome in the cytoplasm of cell. The structures of carbohydrates on S protein and the viral RNA release may present specific pathogen linked molecular patterns identified by the host pattern recognizing receptors such as collectins, C-type lectins, TLR4, and TLR 3. The TLR4 and TLR3 specifically recognize the spike protein, generating an inflammatory response via TRIF and MyD88 mediated processes. The TLR-3 receptor initiates the immune responses to dsRNA throughout the replication of SARS-CoV-2, and the cascades of signaling process are triggered to produce proinflammatory cytokines and type I IFNs. The expression of type I IFN is crucial to enhance the generation of antiviral peptides to protect other cells. The mechanism for presenting the antigen of SARS-CoV-2 is still under observation [5].

The coronavirus infection is related to gene polymorphisms of the mannose attaching lectins, which are also related to antigen presentation. The excessive number of SARS-CoV-2 proteins can interact with signaling of TLR-3 to escape the immune response. The high N-glycosylation of S glycoprotein helps the viral escape from its presentation via MHC, as its presentation stimulates the cellular and humoral immune response. Virus–host cell interactions help the immune mediator's production in high amounts, and large quantities of chemokines and cytokines are secreted in the infected cells against the infection of virus. In endothelial cells, epithelial cells, and macrophages, the inflammasome activation induces the pro-inflammatory cytokines, IL-18 and IL-1b, which participate in the severity and inflammation of COVID-19 symptoms. The carbohydrate-based therapies show that the antibody IgM generation controls the immune responses. An increase of IgA antibodies in the mucosa can be vital strategy to prevent the coronavirus-2 infection [17, 18].

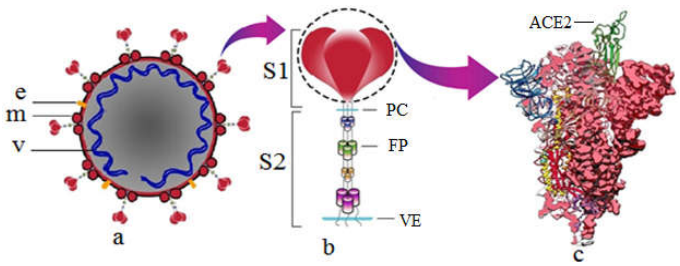

Figure 1. Different Structural components of SARS-CoV-2, a: SARS-CoV-2, b: Spike Glycoprotein, c: atomic level structure of spike glycoprotein, m: Membrane protein, e: Envelope protein, v: Viral genome, S1: Trimeric spike glycoprotein head, S2: Spike protein tail, PC: Protease cleavage sites, FP: Fusion peptides, VE: Viral envelope

SARS-CoV-2and Gut System

The gut is generally the main target of infection for SARS-CoV-2 as its epithelial cells contain high number of ACE-2

receptors and it requires more time to disinfect such a large organ. If gut gets infected the SARS-CoV-2 may be excreted out in feces that could be a source of infection. Generally, the high amount of acid in the stomach can inactivate the virus but the use of antacids can suppress the acid production, SARS-CoV-2 can easily proliferate and infect all parts of gut. The COVID-19 infection may differentiate and activate the mast cells, which releases the cytokines, chemokines, proteases, histamine, and AA derived prostaglandins. The activated macrophages produce IL-1 that stimulates the mast cell to release IL-6, and the IL-1 and IL-6 both cause high inflammation. The histamine can increase the IL-1 production during the inflammatory reaction to amplify the inflammation in lungs [19, 20]. Dendritic cells and macrophages are mainly responsible for forming innate immune responses. B cells, T cells, and Peyer's patches are accountable for the acquired or adaptive immune system and the innate immune system is initiated by the recognition of pathogen-associated molecular pattern through the pathogen recognition receptors [21]. The gastrointestinal tract is also the target of this virus as SARS-CoV-2 was also detected in the stomach, duodenum, and rectum and in the fecal samples of the patients. The two-directional interactions between gut macrobiotic and respiratory mucosa are involved in the pathological immune response to SARS-CoV-2. Intestinal dysbiosis is linked with the high mortality rate in other respiratory infections because of increased inflammation and decreased anti-inflammatory mechanisms in the lung and gut [12].

During the whole lifespan of the host, dynamic and complex-signaling interactions made a relationship between microorganisms and the host. Maternal microbiota starts the intestinal proliferation and colonization in newborns, and the composition of microbiota varies intensely during the early period of life [22]. This microbiota symbiotic balance is susceptible to environmental and intrinsic factors such as the genetic background of the host, diet, use of antibiotics, diet, infectious agents, and allergens, which may change the composition of the microbiota, leading to a dysbiosis[23]. Manly in COVID-19 patients, lungs are infected, but it is also observed that viral RNA is released in the feces of patients, which attracted the attention of researchers to find out the possible fecal-oral transmission route. Increasing studies are indicating communication between lungs and gut microbes, which is responsible for the maintenance of homeostasis and infection development. The severity of infection has majorly related to old ages or patients with medical conditions as the gut microbiota decreases its diversity during aging or under some medical conditions, dysbiosis may be the main reason for older people for severe illness due to COVID-19. Dysbiosis in the gut may increase the gut permeability leading towards secondary infections, which may cause multiple organ failure or can transmit the SARS-CoV-2 from lungs into the intestinal lumen using lymphatic and circulatory systems[24].The disturbance in gut microbiota due to infection can change the signals from normal macrobiotic that can change the immune response, which can cause chronic inflammatory disorder in the lungs and gut. The common lung diseases such as asthma occur with the gastrointestinal disease like inflammatory bowel disease. The patients of chronic obstructive pulmonary disease are 2 to 3 times more susceptible to inflammatory bowel disease and asthma patients also show alteration in their intestinal mucosa. Although the respiratory and gastrointestinal tracts have different functions but they share same embryonic source and structural similarities, so it should not be surprising that these two sites interact with each other in health and disease but the mechanism of interaction need to be explored [25, 26]. The small intestine is generally the main target of infection for SARS-CoV-2 as its epithelial cells contain a high amount of ACE2 receptors, and it requires more time to disinfect such a large organ. If the gut gets infected, the SARS-CoV-2 may be excreted out in feces that could be a source of infection. Generally, the high amount of acid in the stomach can inactivate the virus, but the use of antacids can suppress the acid production; SARS-CoV-2 can quickly proliferate and infect all parts of the gut. The COVID-19 infection may differentiate and activate the mast cells, which release cytokines, chemokines, proteases, histamine, and AA-derived prostaglandins. The activated macrophages produce IL-1 that stimulates the mast cell to release IL-6, and the IL-1 and IL-6 both cause high inflammation. The histamine can increase the IL-1 production during the inflammatory reaction to amplify the inflammation in the lungs [19, 20].

The increased level of pro-inflammatory cytokines due to viral infection in the gut may easily alter the microbial concentration and disturb the intestinal integrity. The malfunctioning of the small intestine may alter the microbial composition in gut and disturb the balance of bidirectional communication between the gut and immune system. Increased level of inflammation in the intestine breaks the gut barrier allowing toxins and antigens to penetrate in the systemic circulation, hence worsening the infection state of patients in COVID-19 [27]. SARS coronavirus infects the lung epithelium as the primary site of action and immune cells. Viral infection like influenza induces Immune responses, which cause changes in gut microbiota, increasing the permeability of the gut that can cause secondary infection[28]. Pathogenic bacteria mostly use the sugars and amino acids for their basic energy needs, which are present in small quantities in a healthy gut. Sometimes good bacteria are killed or suppressed by the frequent use of antibiotics resulting in a sufficient supply of monosaccharides for pathogens generated by host glycans [29]. The structure of monosaccharides supplied by the host can be altered by several signals, such as the use of chemicals, microbial colonization, and the activation of immune cells. In this way composition of organisms and their function can be controlled in the large intestine [30]. The primary food source for the anaerobic microorganisms in the large intestine is plant-based complex polysaccharides. So if these polysaccharides are not available in the diet, they can cause a shift in the overall community macrobiotic and, it continues, over a period of time, can result in loss of that beneficial species from the gut [31].

Carbohydrates and proteins are mostly hydrolyzed and absorbed in the small intestine, in humans and other animals. Bacteria present in the colon utilize remaining food components as an energy source that was not digested in the small intestine (oligosaccharides, non-starch polysaccharides, and resistant starches). This fermentation of residues in the colon produces short chain fatty acids, and numerous gases are released [32]. The short chain fatty acids can directly improve the differentiation of naive T cells into Treg, [33] Th17 and Th-1 [34] and indirectly restrict the Th-2 differentiation [35]. Moreover, SCFAs have a critical effect on the functionality of dendritic cells and neutrophils [36]. Overall colonization resistance of the gut is reduced in the absence of specific beneficial bacteria. When bacteria, depending on polysaccharides are deprived of their diet, they start eating

proteins and mucus, resulting in a reduction of affectivity of defense barrier, which increases the chances of infection by Citrobacter rodentium [37]. A low amount of microbial-accessible carbohydrates in food may cause allergy development by increasing the concentration of cytokines. A polysaccharide-free diet can also promote the easy invasion of *C. dificile*. However, in a study of many pure polysaccharides, it was observed that it is very significant to consider the exact structure and source of the polysaccharides for specific bacteria [38].

Glycosylation based Therapies

The envelope proteins (Hemagglutinin and neuraminidase) of influenza A virus involved glycosylation for several processes such as receptor binding, virus replication, infection and neurovirulence. The addition of carbohydrate may have significant effect on the virus, such as activation or cleavage of hemagglutinin protein through the proteases of host is the preliminary step for entering into a cell. The HIV-1 is a mutagenic virus of the retroviridae whose envelope protein (gp120) is heavily glycosylated protein in nature, with several mannose composition. The loss of glycan eliminates the virus binding to CD4 cell but does not stop their interaction. West Nile virus of the flaviviridae family has become a pathogen of global interest and its envelope protein show crucial role in replication and maturation the virus. The envelope protein E was found involved in many biological processes such as receptor binding, virus assembly and membrane [39]. The enveloped viruses contain an integral envelope protein which is responsible for host cell interactions, like receptor binding, internalization of virus and infectivity. For example, the infectivity and intracellular transport of hepatitis C is majorly affected by glycosylation [40]. Newly emerging viruses like Ebola, Hantaan, Hendra, Newcastle, metapneumovirus, Nipah and coronaviruses have shown glycosylation with important roles in protein folding and infectivity [41].

Carbohydrates being independent of T cells, generate poor immunity, so for vaccine development, a protein carrier is conjugated with polysaccharides. This conjugation produces T-cell dependent response, which forces the adaptive immune system to produce IgG antibodies and generates memory to produce antibodies for specific carbohydrate moiety [42]. This method generates antibodies against the bacteria of carbohydrates origin, such as *Haemophilus influenza* type B vaccine. Glycoproteins also have the significant character in protease protection, cell adhesion, signaling transduction, and biological process as in the case of CoV-2, so these proteins may be the best candidate for immunization [43]. Soluble oligosaccharide from the human cell surface is widely studied for anti-infective drug development as these are good candidates because of their molecular weight and non-immunogenic characteristics [44]. Many organisms such as bacteria, viruses, and their released toxin need to bind by cell surface carbohydrates to start infection [45]. Polysaccharide-based vaccines are more efficient for disease prevention, such as ActHIB, a conjugate vaccine is used for the prevention of meningitis in children, the Prevnar is used for the prevention of pneumococcal infections and the typhim Vi is used for tourists in countries with poor sanitation standards. Many synthetic glycopeptides are being used for the chemical modification of cancer cell's glycan to develop vaccines against specific cancer by stimulating more immune responses against the carbohydrate antigen as tumor-associated carbohydrate antigen is considered as a foreign material, so its response is feeble, and it is almost ineffective to remove the cancer cell. Many vaccines relying on the monoclonal antibodies production for tumor-related carbohydrate antigens are being studied against various types of cancer [46-48].

Conclusion

Its spike protein binding which initiates the infection of SARS-CoV-2 with the ACE2 receptor; hence the glycosylation of spike protein has the main character in its adherence to cell surface which can be modulated to control the infectivity. The ability of carbohydrates to interact with the immune system and ease of modification through different methods creates an excellent opportunity to develop vaccines with enhanced efficacy against various diseases. A good diet to avoid gut dysbiosis may boost the immune system and provide enough nutrients to reduce the susceptibility to infection. The infection in the gut and lungs are interlinked, the mechanism of communication between respiratory and gut microbiota still needs investigations, but infection in the gut can affect the respiratory system. Understanding these interactions between host cells and spike protein may help develop the vaccines better so that new strains of viruses can be treated effectively.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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