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REVIEW

The pivotal roles of the host immune response in the fine-tuning the infection and the development of the vaccines for SARS-CoV-2

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ABSTRACT

SARS-CoV2 infection induces various degrees of infections ranging from asymptomatic to severe cases and death. Virus/host interplay contributes substantially to these outcomes. This highlights the potential roles of the host immune system in fighting virus infections. SARS-CoV-2. We highlighted the potential roles of host immune response in the modulation of the outcomes of SARS-CoV infections. The newly emerged SARS-CoV-2 mutants complicated the control and mitigation strategies measures. We are highlighting the current progress of some already deployed vaccines worldwide as well as those still in the pipelines. Recent studies from the large ongoing global vaccination campaign are showing promising results in reducing the hospitality rates as well as the number of severe SARS-CoV-2 infected patients. Careful monitoring of the genetic changes of the virus should be practiced. This is to prepare some highly sensitive diagnostic assays as well as to prepare some homologous vaccines matching the circulating strains in the future.

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Introduction

The coronavirus infectious disease-19 (COVID-19) is a newly emerged coronavirus discovered in late 2019[1]. The etiology of this syndrome is severe acute respiratory syndrome-2 (SARS-CoV-2).[2] The WHO declared that SARS-CoV-2 is the causative agent of the recent modern pandemic across the globe on March 11th, 2020.[3] SARS-CoV-2 belongs to the subgenus Sarbecovirus, subfamily-*Orthocoronavirinae* within the family *Coronaviridae*, and the order *Nidovirales*. This is the seventh identified human coronavirus. The genome structure and organization of SARS-CoV is very much similar to other coronaviruses, belongs to the Betacoroanviruses along with some other important zoonotic coronaviruses (MERS-CoV and the SARS-CoV). However, the genome sequencing analysis revealed some variation among those viruses across their genomes, particularly the spike glycoprotein (S). The virus genome is a linear single-strand RNA molecule (~ 30-kilobases) in length. The 5′two-third of the viral genome encodes the non-structural proteins, which are responsible for replication and pathogenesis, immune evasion properties of viruses. While, the 3′ third of the viral genome encodes four essential proteins (spike glycoprotein (S), the envelope, the membrane (M), and the nucleocapsid proteins (N)) interspersed by some minor non-structural proteins. Some of these proteins play essential roles in the virus replication cycle, immune response, and immune evasion strategies possessed by the virus to hijack the host immune response. The course of SARS-CoV infection may be developed into three subsequent stages. This classification is mainly based on the clinical signs and the viral loads in the collected samples from tested patients.[4] During the first stage, the infected individual does not show any visible clinical signs and may have little or no viral load in their secretions. In the second stage, the patient starts to show apparent clinical manifestations with moderate viral loads detected in their secretions. In the final third stage, the affected individuals suffered from severe conditions, including the involvement of the lungs and many other organs (kidneys and intestine).[4] The outcomes of the infection are mainly fine-tuned by the immune status of the infected patients. The host immune response for the SARS-CoV-2 is developed in two phases.[5] The first phase is triggered during the acute stage of the infection to enhancing the immune response in overcoming the viral infection. While the second phase started with the progression of the inflammatory reactions and damage of the target organs which may lead to the death of the infected patient.[5]

The biology of the SARS-CoV-2 is contributing to the control and mitigation of the virus infection and pathogenesis

SARS-CoV-2-S protein is one of the leading viral proteins that play essential roles in the virus cycle, identification of the viral tropism, especially during the virus attachment, and the procedure of viral entry into the cell. It is one of the main targets for the vaccine,

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therapy, and diagnostic assays for most coronaviruses, including SARS-CoV-2. The viral cycle starts with the attachment of the spike glycoprotein with the viral receptors, the angiotensinogen converting enzyme-2 (ACE-2). Some other cellular factors favor virus entry, such as basigin (BSG). This is a newly discovered mechanism for the SARS-CoV-2 entry (CD147-SP).[6] The S protein is inert outside the host, which undergoes activation through the furin enzyme cleavage into the S1 and S2 subunits.[7] This step is crucial for the success of SARS-CoV-2 infection on the cellular level. Blocking the cleavage of the spike glycoprotein will inhibit the virus infection, thus representing an attractive potential target for drug design. The furin enzymes are highly expressed in the respiratory tract; thus, once the virus exits from one cell, it will be ready to enter another cell and potentiate the virus replication.[8] Preventing the SARS-CoV-2 virus attachment to the host cells can be done by several strategies. Using some fusion protein inhibitors is a promising trend in halting the SARS-CoV and MERS-CoV infection both *in vitro* and *in vivo* in mouse models.[9] Another important host factor is the transmembrane protease, serine 2 (TMPRSS2), which potentiates the viral infection by exposing the active sites of the spike glycoprotein to interact with the host cell and mediates the virus entry.[10] Using the TMPRSS2 inhibitors recently proved to prevent the SARS-CoV-2 entry into the target cells. This is a new promising trend in the treatment of SARS-CoV -2.[10] Another essential protein is the main protease -chymotrypsin-like cysteine protease ($3CL^{pro}$). It plays an essential role during coronavirus replication. The sequence of this protein is most likely highly conserved among most coronaviruses. Using some 3 CL pro inhibitors such as ledipasvir showed promising results in the inhibition of the SARS-CoV-2 replication.[11] This is one of the promising therapeutic approaches for COVID-19 with minimal side effects.[12] The N protein binds to the viral nucleic acids to form the nucleocapsid from which it acquires its name. This protein plays some essential roles during virus replication.[13] This protein is highly phosphorylated, thus potentiates the binding with the viral RNA compared to other RNA molecules.[14] The immune response plays an essential role in fine-tuning the outcomes of any infection with different pathogens. There are two arms of the immune response; the innate and the adaptive responses. In the following sections, we will elaborate on some recent advances on the immune response against SARS-CoV-2, including the humoral as well as the cell-mediated immunity.

The adaptive immune response in the context of SARS-CoV2 infection

Typically, the adaptive immune response plays an important role in controlling and clearing several viral infections.[15] There are two types of reactions involved in adaptive immunity, including the cellular immune response, which is mediated by the T cells, and the humoral immune response, which is an antibody-mediated response.

The T cells mediated immune response

During the coronavirus infection, the antigen-presenting cells (APC), such as dendritic cells (DCS), can pick up the viral peptides and presented them in the context of the major histocompatibility (MHC) class-2. Subsequently, the CD4 + T cells (T helper) can recognize these peptides and then subsequently being activated. Therefore, they produce several types of cytokines and chemokines. The cytokines produced by the CD4-T cells including several subsets (Th1, Th2, Th17, and T regulatory cells (T-regs)). The Th1 cells produce IFN-γ, whereas the Th2 cells produce some cytokines such as IL-4, IL-5, and IL-13 (Figure 1). The T-reg cells usually produce some suppressive cytokines such as IL-10 and TGF-β. They have an essential role in the regulation and maintaining the immune response and therefore preventing autoimmunity.[16–18] Th17 producing some cytokines, including IL-17, IL-21, and IL-22.[19] Furthermore, the CD4 + T cells are activating the CD8 + T cells by providing a co-stimulatory signal.[20] This stimulation is achieved through the interaction between the CD40L and the CD40 on the DCS. This interaction induces an up-regulation of some ligands, including CD80 and CD86. Both are expressed by the DCs, which came in contact with the CD28 expressed by the naive CD8 T cells.[21] CD4 + T cells stimulate the B cells to produce some specific antibodies.[22] Furthermore, the CD8 T cells can destroy the virus-infected cells.[22] It has been shown that in the case of SARS-CoV patients, the CD8 T cells play an important role in the destruction and clearance of the infected cells within the pulmonary interstitium tissues.[23] Moreover, the MERS-CoV infection of mice deficient in both T and B cells showed that the virus was not cleared from the lungs in the absence of T cells compared to control animals. This suggested the importance of T cells in the clearance of coronavirus infections.[24] SARS-CoV infection in some CD8 deficient mice did not affect the viral load. Whereas depletion of the CD4 T cells resulted in the delay in the viral clearance and was associated with a marked reduction in the cytokines production. It also reduced the production of the viral-specific neutralizing antibodies as wells as a marked reduction in the recruitment of lymphocytes into the lung tissues. This suggests the pivotal role of the CD4 rather than the CD8 during the early stages of the SARS-CoV infection.[25] One study conducted on 128-SARS-CoV survived individuals revealed the convalescent samples showed that the CD8 + T cell was higher and more prominent than the CD4 + T cell. The severely affected individuals developed higher levels of central memory T cells and were associated with a higher functional activity of both CD4 and CD8-T cells. This pattern was in comparison to the mildly and moderately affected group of patients who showed a strong T cells response in about 70% of cases. This is in addition to, high level of specific antibodies against most of the structural proteins of the virus, including (S, E, M, and N). However, the Th2 cytokines, including IL-4, IL-5, and IL-10, were highly expressed in more severe and fatal cases.[26] Surprisingly, the role of Th17 during the SARS-CoV infection was not fully defined yet. However, the IL-17 levels were elevated in the serum of some COVID-19 patients.[27] The SARS-CoV-2 infection triggered an exaggerated immune response in the infected patients called cytokines storm (Figure 1) or macrophage activation syndrome (MAS).[28] It is may also be known as secondary haemophagocytic lymphohistiocytosis (sHLH).[29] This condition may lead to acute respiratory distress syndrome (ARDS), which contributed substantially to the outcomes of the virus infection in diseased individuals.[28]

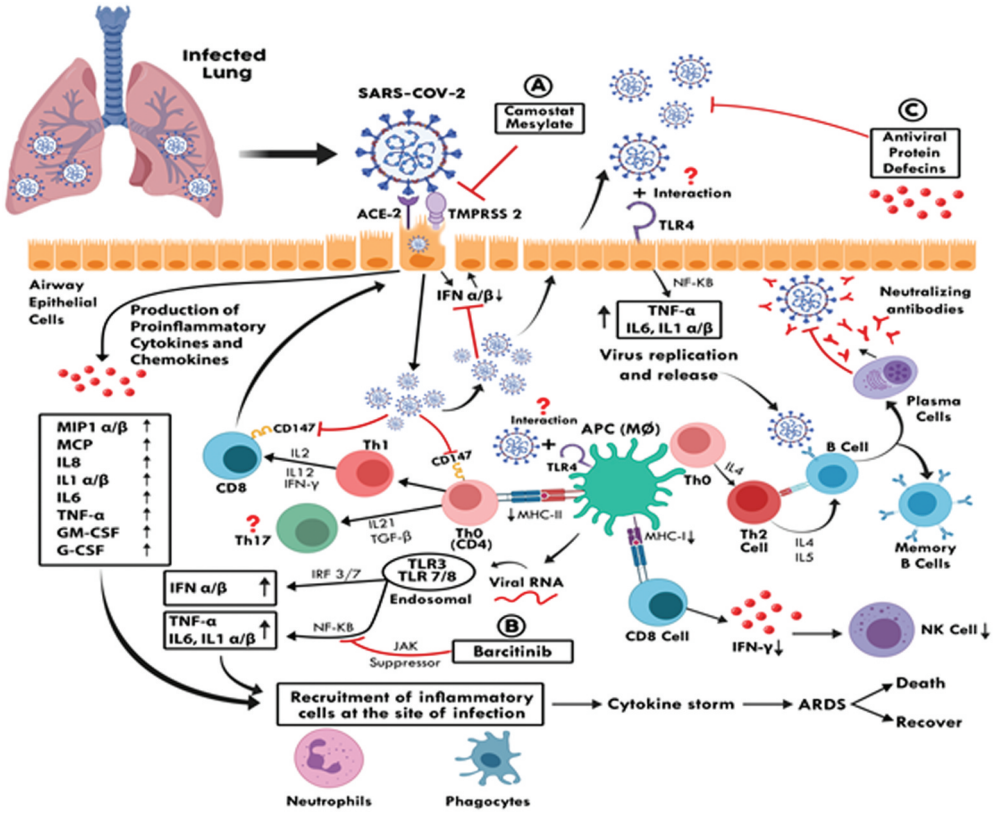

Figure 1. The proposed diagram of the innate and adaptive immune response to SARS-CoV2 infection.

Cytokine storm and the severity of COVID-19

Moreover, there is a direct relationship between the cytokines storm and the severity of COVID-19 infections and fatal outcomes.[30] During severe COVID-19 cases, both IL-6 and IL-1 levels are dramatically increased compared to the mild or moderate groups of patients. This pattern suggests the important roles of this cytokine as a marker for the severity of clinical cases. It may also have used in assessment and the prognosis of the SARS-CoV-2 infection.[31,32] Therefore, targeting IL-6 or its receptor (IL-6 R) with specific monoclonal antibodies, such as (Tocilizumab, Siltuximab) may result in reducing the severity of the airway inflammation and consequently reduce the severity of the disease.[33] Further studies are required in order to enrich our understanding of the interaction between SARS-CoV2 and the host cells. This may lead us to achieve better knowledge in regard to the cytokines response mediate by the host-infected cells and how may the virus escape from the immune recognition. Moreover, one study was conducted on the peripheral blood mononuclear cells (PBMCs) isolated from SARS-CoV recovered individuals. This study showed that SARS-specific memory T cells against most viral structural proteins, including membrane (M) and Nucleocapsid (N) protein, were detectable up to 11 years after SARS-CoV infection. These findings suggestion the SARS-CoV recovered patients may be protected against the subsequent re-infection with homologs viral strain.[34] This may support the theory of vaccination against SARS-CoV as an important aid in the prophylaxis of such viruses and their related viruses.

Both SARS-Co-V and SARS-CoV-2 can directly infect both the macrophages and the T cells, which contributed substantially to the pathogenicity of these viruses.[33,35] Recent studies on some SARS-CoV-2 patients showed that the number of both CD4 + T and CD8 + T in the peripheral blood sharply decreased, although their status remained active, and the CD8 + T cells are becoming more cytotoxic.[36] Thus, there is an urgent need to fine-tune and control the CD8 T cell responses to minimize and avoid as much as possible any lung tissue damage and injury. Additionally, it has been revealed that the number of the T cells was decreased in the case of the severely affected SARS-CoV-2 patients, including the TH and the T reg cells. Whereas, the percentage of naïve Th cells was increased, and the memory Th was decreased in severe cases of SARS-CoV-2 infection.[37] T cells were reported to express the SARS-CoV-2 receptors, such as ACE-2 and CD147.[33,37] This might be one of the main reasons behind the dramatic decrease in the total numbers of T-cells count in the case of the severely affected SARS-CoV-2 patients.

Mapping and identification of neutralizing epitopes in SARS-CoV-2 and its applications in the vaccines and diagnostic assays development

During MERS-CoV infection, the CD8-T-cell production was largely increased during the early stage of the infection and was usually associated with severe cases of infection; however, during the recovery phase, the Th1 cell was notably observed.[38] Interestingly, both SARS-CoV and MESR-CoV can produce specific CD4 memory cells against some conserved epitopes shared by both viruses. Therefore, mice were protected against the challenge of the wild types of these viruses. These shared epitopes induce neutralizing antibodies

that can cross-react with MESR-CoV and SARS-CoV, suggesting the potential role of these conserved peptides as vaccines against most of the coronaviruses.[39] Since most of these epitopes recognized the antigenic counterparts within most structural proteins of both SARS-CoV and MERS-CoV, a similar approach may be adopted in the case of the SARS-CoV-2. Mapping these neutralizing epitopes within the three viruses (SARS-CoV, MERS-CoV, and SARS-CoV-2) may pave the way for several potential vaccines against SARS-CoV-2. In a similar trend, it may highlight the promising trends of using serum and plasma of the recovered patients as potential therapeutic interventions against SARS-CoV-2 infection. A new study showed a promising trend of using some single antibody domains isolated from Illama immunized with the coronaviruses spike protein in vitro.[40] These potent antibodies protected the cells from infection with the SARS-CoV-2 infection by preventing the virus entry into the cells.[40]

In conclusion, although the three coronavirus candidates (SARS-CoV, MERS-CoV, and SARS-CoV-2) are belonging to the same family, there is a differential display of their downstream immunological profiles, which contribute to the severity and outcomes of the viral infection for each virus.

The B cells mediated immune response

The B cell immune response plays key role in the protection against the subsequent SARS-CoV-2 infection through the production of viral-specific antibodies.[41] These antibodies were able to neutralize the viral infectivity, therefore, prevent the virus attack to the host cells.

Although few serological studies were conducted on the SAR-CoV-2 at this time, some studies were conducted to monitor the antibody levels in some patients. These studies showed that the specific IgM antibody reached its peak 9-day post-infection. While the IgG level increased in about two weeks and lasted up to 20 days after infection. The serum containing antibodies collected from confirmed COVID-19 patients appeared to cross-reactive with SARS-CoV and not with other coronaviruses members. Moreover, *in vitro* studies on sera from those patients were also able to neutralize the SARS-CoV infectivity in cell culture. This suggests cross-reactivity between both SARS-CoV and SARS-CoV-2.[33] Another study was conducted on one patient infected with SARS-CoV-2 to monitor the curve of neutralizing antibodies of IgM and IgG classes against (S) and (N) proteins of SARS-CoV. This study revealed that the level of these antibodies in sera of this patient was low on day four after infection, which increased at day 9, then dropped to non-detectable levels on day 20 in the case of IgG.[42] In the same context, another independent study also reported that at day 0, the titters of the IgM and the IgG were undetectable or even very low then increased by the fifth day of infection, whereas the IgG levels were increased in all the patients.[43] However, in the case of SARS-CoV infection, the starting of the antibody production against the virus is varied among different classes of antibodies. In the case of IgM, it ranged from 3 to 42 days post-infection. Whereas in the case of the IgG, it ranges from 5 to 47 days.[44] In conclusion, there is a differential display in the kinetic of various classes of antibodies between SARS-CoV and SARS-CoV-2. These data may explain at least in part the differential clinical outcomes of infection of those two viruses.

Immunity to the reinfection in the context of SARS-CoV-2

It is not clear whether the primary infection with SARS-CoV-2 may provide long-term protection against the re-infection or not yet. The re-infection of monkeys on day 28 after the initial SARS-CoV-2 infection revealed the same result in the protection of these animals against the second round of infection with the virus (Figure 1).[45] This was suggesting the potential roles of the immune response in the protection against re-infection with the SARS-CoV; however, these findings require further clarification in case of human infection. Thus, longitudinal cohort studies are urgently required to clarify whether the primary SARS-CoV-2 infection may provide enough long-lasting protection upon any subsequent infection.

Applications of convalescent sera and monoclonal antibodies in the treatment of COVID-19

The human convalescent serum is considered a potential opportunity for the treatment of COVID-19 patients. This may be achieved through the collection of sera from the recovered COVID-19 patients where the neutralizing antibodies are present against SARS-CoV-2 and administered to some new patients to help them overcome the active infection, especially in the more severe cases.[46] Additionally, it has been reported that the administration of SARS-CoV-2 convalescent sera from recovered patients helped in the alleviation and subsidy of severing active COVID-19 infections.[31,47] Although human convalescent serum is a promising approach in the treatment of SARS-CoV-2 infection, there are some limitations related to this method. These concerns include the possibility of transferring other pathogens to the recipient patients, the potential activation of some antibody-dependent enhancement (ADE). This process may suppress the anti-innate immune responses as it was reported in some *in vitro* studies done earlier on SARS-CoV.[48] Other factors related to the adjustment and fine-tuning of the administered volumes, titers, and time of transfusion of plasma from the donor to the recipient patients.[49] The convalescent serum approach, using passive immunization by specific monoclonal antibodies is more specific, safe, and has a low risk of transfer other potential pathogens. Furthermore, using cocktail monoclonal antibodies (Mab) of the SARS-CoV -2 that are able to recognize several epitopes may increase the efficiency of these neutralizing (Mab) antibodies.

Kinetics of SARS-CoV-2 memory cell responses

Regarding B cell response, a recent study reported that all serum patients relative to uninfected controls had a significant proportion of specific B memory cells against RBD and NCP. These B cell populations have both unswitched class (CD27+ IgM IgD) and switched class cells (CD27+ IgD) which contained IgG expressing B memory cells.[50] Effective and predominant B memory cells response are induced by SARS-CoV-2 infections, which contained IgM and IgG-specific B memory cells against RBD and NCP. Furthermore, the B memory cells against RBD are nearly CD27+ and correlated positively with T follicular helper cells (Tfh).[50] Serum antibodies have decreased gradually following

SARS-CoV-2 clearance. However, specific memory B cells are detected over time in a stable proportion.[50]

It has shown that memory response against SARS-CoV-2 lasts for 8 months and spike-specific IgG antibodies were stable and circulated for up to 6 months post-SARS-CoV-2 infection. Also, B memory cell counts were abundant at 6 months rather than the first month especially post-viral symptoms appearance. The proportion of RBD-specific IgG was 88% between 6 and 8 months.[51] On the other hand, IgA levels were assessed in most COVID-19 patients, started to increase on day 27, and disappeared by 3 months. B cells appeared on day 16 early after the onset of viral symptoms and increased and become stable in the following 4–5 months.[51] 10–30% of memory B cells in recovery patients were specifically for RBD antigens. Antibody titers (IgG) decreased after 6–8 months post symptoms onset among individuals but is highly heterogeneous among them.[51] Another study has demonstrated that CD19 + B cell numbers were higher in severe COVID-19 than mild cases. Memory B cells were low in severe and critical cases, but the plasma cells were high, due to the disease severity. Overall the total number of B cells in COVID-19 patients (different categories (mild, severe, and critical) was lower than healthy donors, suggesting that preexisting memory B cells specific for other coronavirus were activated and differentiated to atypical memory ($CD27^{-}$) and/or plasma cells.[52] Taking together, memory B cells might be represented the long-lived humoral response than serum antibodies and could be used as robust and substitute markers of humoral immunity in immunization studies.[50] In contrary to other studies that reported a decrease in B cell numbers during COVID-19,[53,54] there was no reduction of B cells in all patients and serum that collected within 14 days of symptoms appearance.[50]

Based on the presented research about the SARS-CoV-2 memory cells, it is concluded that both previous infections and vaccination against the virus may provide a considerable level of immunity against the virus however, large-scale studies are required to map the kinetics of the memory cells among the infected and vaccinated individuals.

Some SARS-CoV-2 immune evasion strategies

Both SARS-CoV and MERS-CoV evade the immune response in many ways.[23,55] Here, we are presenting some immune evasion strategies posed by those closely related viruses to the SARS-CoV-2. These evasion strategies help the SARS-CoV-2 to hijack the host immune response and contribute to the progress and promotion of its replication cycle. These strategies may also contribute to the lethality and virulence of SARS-CoV-2 infected patients. The SARS-CoV-2 induces severe pathology in many vital organs of the affected patients, especially lungs, kidneys, and, heart, brain, intestines.[36] There might be some virulent virus factors produced by the virus to induce this multi-organ failure.

Meanwhile, the SARS-CoV-2 utilizes some unique immune evasion strategies that may contribute to the virulence and lethality of this virus. Recent studies revealed SARS-CoV-2 infection-induced differential display of some crucial blood and immune markers. The infected patients had an increase in the neutrophils, IL-6, and the serum reactive protein (CRP). However, those patients showed a 35% reduction in the total numbers of circulating lymphocytes.[56] These parameters act as biomarkers for the SARS-CoV-2 infection. They may be used for monitoring the progress of the treatment of infected patients. Both SARS-CoV and MERS-CoV possess some immune evasion strategies through the production of the double-membrane vesicles, which contain the virus replication complex. Those viruses escape the host immune system detection through the replication inside these vesicles.[57] Another interesting phenomenon is the inhibition of the IFN-I pathway by the MERS-CoV- ORF-4a.[58]

Furthermore, both MERS-CoV and influenza virus (H5N1) decrease the expression of the antigen presentation.[59] The SARS-CoV-2 infection triggers similar pathways to ensure the success of its replication cycle; however, further studies are required to confirm these findings. In the same context, the MERS-CoV- 4b interferes with the NF-κB pathway resulting in the counteraction of the host's innate immune response against the virus infection.[60] A new study showed the coexistence of the viral RNA in saliva and specific antibodies in sera of patients recovered from SARS-CoV-2 for up to 40 days after the recovery of some infected patients. These findings suggest some unique immune evasion strategies adapted by the virus to hijack the host immune response, thus remain active even after the recovery of the patient.[61] More studies are required to confirm these findings and to reveal the mechanism behind these phenomena.

Roles of various SARS-CoV-2 proteins in the immune evasion and hijacking the host immune response

Recent studies showing that various SARS-CoV-2 proteins including some structural and the nonstructural proteins may contribute to the virus immune evasion strategies (Table 1) which enhance the virus replication and promotes its pathogenesis and spread.[62,63,65,67,69,70] SARS-CoV-2-ORF8 plays important functions during virus replication and in viral immune evasion.[67] This may affect the downstream pathogenesis of the virus. It mediates the degradation of the MHC-class -I and contributes to the marked inhibition of the IFNs production. These effects fine-tune the outcomes of the virus infection.[67] SARS-CoV-ORF-3 plays an important role during the virus infection and pathogenesis through its actions on the JAK-STAT, chemokine, and cytokine- pathways.[66] Mutations within the SARS-CoV-ORF-3 are associated with high case fatality rates among the affected individuals.[66] Both SARS-CoV-2-NSP-2 and NSP-6 act synergistically to inhibit the INFs production in a much more efficient way than the SARS-CoV and MERS-CoV.[63] There is an active interaction between the NSP16 and the NSP-10 in the context of SARS-CoV-2 infection. This interaction creates some unique binding pocket sites for the virus activation and contributes to the viral immune evasions.[65] SARS-CoV-NSP-1 binds to various host cell ribosomes subunits resulting in the shutdown of some host cell genes both *in-vitro* and *in vivo*.[62] SARS-CoV-2-ORF-9 C is a transmembrane protein that recently showed to play important immune evasion roles during the virus infection.[71] It is the first coronavirus-ORF-9 C to induces its downstream effects

Table 1. Summary of some immune evasion effects of various SARS-CoV-2 proteins.

N	Protein	Type	Immune evasion effects	Ref
1	NSP-1	NSP	Binds to ribosomal subunits resulting in the shutdown of some host cell protein synthesis	62
	NSP-2	NSP	Inhibits IFNs production	63
2	NSP-3 (PLp)	NSP	Post-translation modification of host cell proteins Affect the NFKb and IFNs pathways	64
3	NSP-6	NSP	Inhibits IFNs production	63
4	NSP-10	NSP	Contribute to the formation of the unique binding pocket sites with NSP-16	65
5	ORF3	NSP	Affect the JAK-STAT, chemokine, and cytokine- pathways	66
6	ORF8	NSP	Degradation of the MHC-I Inhibition of the IFNs pathways	67
7	NSP-15	NSP		
8	NSP-16	NS	Contribute to the formation of the unique binding pocket site with NSP-10	65
9	S	SP	Conformtionalcahnges and glycosylation enable the spike protein to induce evasion of the host immune response	68
10	M	SP	Possesses sugar transporter-like to enhance virus replication and immune evasion	69

NSP = none structural protein.
SP = structural protein.

through tackling the interferon signaling pathways.[68,69] The SARS-CoVNSp-15

Play important roles in the RNA processing and host immune evasion. Repurposing of some drugs using the in silico analysis showed that targeting the NSP-15 of the virus may have promising trends in the control of SAR-CoV-2 infection.[72] SARS-CoV2-PLpro (papin like protease) plays important role in the process of post-translation modification of viral and host cell proteins. It also contributes to the regulation of the IFN and NFKB pathways which enhancing the progression of virus replication and immune evasion.[64] Thus, targeting this protein may represent one of the promising trends in controlling virus infection within the host.[64] The SARS-CoV-2-S protein undergoes a process of posttranslational glycosylation which plays important role in the virus infection, pathogenesis, and host immune system evasion.[68] Recent studies showing the SARS-CoV-2-M protein possesses sugar transporter-like which have a substantial impact on virus replication and host immune evasion.[69]

SARS-CoV-2 vaccine candidates

Since the emergence of SARS-CoV-2, scientists all over the world and vaccine development companies are in a battle working day and night to achieve this milestone. The rationale behind the vaccination strategy is to immunize the at-risk people, especially the immunocompromised, elderly, and health care workers in the front line of combating this virus. Although there are six other human coronaviruses identified from long time, there are no available licensed vaccines against any of them despite some new trials for vaccines against MERS-CoV recently developed and are in the clinical trials.[73,74] Typically, vaccine development is a lengthy procedure and requires many steps, including laboratory testing preclinical and clinical trials. At this time, to speed up the procedures of making successful SARS-CoV-2 vaccines. Perhaps some of the preclinical studies were performed in parallel with clinical trials; however, many obstacles were hampering these procedures, such as the regulatory authorities must assess the vaccine manufacturing process and preclinical data to ensure the safety of volunteer persons.[75]

History of the development, testing, evaluation, and approval of some SARS-CoV-2 vaccines

There are many strategies for vaccine preparation and development for many viruses. Some of these strategies may be applicable for coronaviruses, including (i) the live-inactivated, (ii) the subunit vaccines, and (iii) the nucleic acid-based vaccines. On Jan 23rd, 2020, the Coalition for Epidemic Preparedness Innovations (CEPI) has declared the funding to develop some vaccines against SARS-CoV-2 using three different approaches, including DNA, mRNA, and molecular clamp.[76] As of April 2020, more than 20 potential SARS-CoV-2 vaccine candidates have been published worldwide (Table 2). As of April 2020, several COVID-19 vaccine candidates were approved and currently in the clinical trials at different phases. Currently, there are at least 10 SARS-CoV-2 approved vaccines and deployed in many parts across the world. Finally, we now have several SARS-CoV-2 vaccines approved and deployed in one of the largest global vaccination campaigns ever. As of Dec 23rd, 2020, there are 2013 vaccine candidates for SARS-CoV-2 under development. Almost 44 out of them are in varying stages of the clinical trials.[86] A strong network of international coordination and cooperation between academia, vaccine developers, public health institutes, and government bodies urgently needed to make sure that an effective vaccine may be developed as soon as possible to stop the spread of SARS-CoV-2 across the globe thus the current SARS-CoV-2 pandemic can be contained.

Some potential nucleic acid-based SARS-CoV-2 vaccines

The nucleic acid-based vaccines are the most advanced platforms for the response to emerging viral pathogens. For example, during the Zika virus outbreak, nucleic acid-based vaccines were the first vaccine candidates that entered clinical trials in less than 1 year after the emergence of the epidemic.[87] Some SARS-CoV-2 nucleic acid-based vaccine platforms are developed. The Moderna Therapeutics, CureVac, and Shanghai East Hospital (Tongji University) Stermirna Therapeutics are exploring the mRNA vaccine platforms.[56]

Table 2. Top ranked SARS-CoV-2 vaccines.

N	Platform	Current status	No of doses	Prime post intervals/days	Current status	Country of origin	Storage temperature	Efficacy*	Ref
I	**mRNA vaccine**								
	1	BioNTech/Fosun Pharma/Pfizer	2	28	Deployed	USA, Germany, China	(−80) °C	95%	77
	2	Moderna/National Institute of Allergy and Infectious Diseases	2	28	Deployed	USA	(−15/-20) °C	94.1%	78
II	**Recombinant viral vector vaccines**								
	1	Astra-Zeneca	2	28/84	Deployed	UK	2–8°C	50.4%	79
	2	CanSino Biological Inc	1	N/A	Phase III	China		96.1%	80
	3	Johnson & Johnson	2	56	Deployed	USA	2–8°C	−50.4% in symptomatic -78% mild cases -100% severe cases	81
	4	Sputnik-V	2	21	Deployed	Russia	2–8°C	92%	82
III	**Inactivated vaccines**								
	1	Sinovac	2	14	Deployed	China	4°C		83
	2	Sinopharm	2	21	Deployed	China	°C	86	84
IV	**Subunit vaccines**								
	1	Novavax	2	28	Phase III	USA, UK, South Africa	(−70) °C	−96.4% /original strain -86.3 /UK variant -48.6%/SA variant	85

*Efficacy mainly based on the prevention of severe COVID-19 syndromes but not the SARS-CoV-2 infection.

Some SARS-CoV-2 mRNA deployed vaccines

The mRNA-1273 vaccine was developed by Moderna Therapeutics and the US National Institute of Allergy and Infectious Diseases (NIH).[88] This COVID-19 vaccine RNA-1273 is an mRNA vaccine expressing COVID-19 spike protein. This vaccine phase I clinical trial was initiated at Kaiser Permanente Washington Health Research Institute (KPWHRI) in Seattle. Simply, the vaccine was constructed to encode the SARS-CoV-2 gene and encapsulated with lipid nanoparticles for delivery into the host cells.[89] This vaccine showed a high degree of prevention of the severe COVID-19 cases up to 94.1% (Table 2). This was a great leap for lowering the number of hospitalizations among infected patient especially severe cases require admission to the intensive care units.[89] Another promising vaccine is the BNT162b2 mRNA. This vaccine developed through the nucleoside-modified RNA encoding the full-length SARS-CoV-S gene coupled with some lipid nanoparticle.[77] This vaccine is showing 95% protection against the development of severe COVID-19 cases.[77]

Both vaccines are currently deployed in many parts int eh world. They administered on a prime-boost regimen 21 days apart.[90]

Some recombinant SARS-CoV-2 vaccines

Another approved vaccine established by the Cansino Biologics Inc, the Academy of Military Medical Sciences of China, named Ad5-nCoV. This vaccine is mainly based on a vector containing a defective adenovirus-5 that expresses the spike protein of the SARS-CoV-2. Finally, the University of Oxford in combination with AstraZeneca company, developed and deployed the ChAdOx1-nCoV-19 vaccine.[91] This approach has been used recently to develop a vaccine against MERS-CoV.[73] This ChAdOx1-nCoV-19 vaccine showed promising results in protecting some rhesus macaques from experimental infections with the SARS-CoV-2.[88] The clinical human trials for these vaccines showed a high rate of protection (88%) against the severe COVID-19 cases when administered in a prime-boost regimen (Table 2).[91] These studies suggested that the maximum performance of this vaccine can be achieved in a prime-boost regimen 28 days apart.[92]

Some potential live virus and recombinant SARS-CoV-2 vaccines

One potential common vaccine candidate for coronaviruses may be developed based on the similarities between the T-cell epitopes of SARS-CoV and MERS-CoV. It may also depend on the possibility of cross-reactivity between these viruses.[43] A recent study identified some candidate vaccines design based on the high degree of genetic similarity between the SARS-CoV and the SARS-CoV-2.[93] By screening SARS-CoV-derived B and T cell epitopes, they identified some promising candidates derived from the spike (S) and nucleocapsid (N) proteins that showed a high degree of similarity to SARS-CoV -2 proteins.[93] It is well documented that the spike (S) glycoprotein or S protein is the primary inducer of neutralizing antibodies and T-cell responses in several SARS-CoV vaccines. This includes the use of full-length S protein or S1 receptor-binding domain (RBD) and expression in virus-like particles (VLP), DNA, or viral vectors.[94] The Johnson & Johnson Company has recently released its SARS-CoV-2 vaccine using the Janssen's-AdVac® adenoviral vector used previously to develop their Ebola virus vaccine. This vaccine has been approved by many countries. The University of Hong Kong has also launched a modified nasal spray influenza vaccine expressing a surface antigen from the SARS-CoV-2 protein. Besides, Codagenix has established a "codon de-optimization" vector method to abolish the virus virulence and to explore this SARS-CoV-2 vaccine strategy.[95] This type of vaccine has proven to be highly effective and provides long-lasting protection.

One of the significant advantages of the whole virus vaccine is the activation of the T-cells responses, including $CD4^+$ and $CD8^+$ T, offering specific neutralizing antibodies, and memory B cell responses. Furthermore, it can trigger toll-like receptors (TLRs), such as TLR 3, TLR 7, TLR-8, and TLR 9. However, the attenuated pathogen may cause disease, as was reported with the oral polio vaccine.[96] A recent study used the recombinant parainfluenza virus-5 (PIV-5) backbone for the delivery of the MERS-CoV-S protein. This study showed excellent protection of the mice challenged with lethal MERS-CoV after a single intranasal administration of this recombinant vaccine.[97] This approach could be one of the new promising vaccination approaches for the SARS-CoV-2.

SARS-CoV-2 inactivated vaccines

The inactivated vaccine is one of the classical vaccination strategies developed a long time ago and was applicable for many pathogens, including respiratory pathogens such as the influenza virus.[98] One of the main advantages of this approach is the preservation of the spike protein conformational epitopes in their original forms. This will result in the production of specific neutralizing antibodies against the original virus, as in the case of MERS-CoV.[98] Several inactivated SARS-CoV-2 vaccine candidates were tested for their efficacy and side effects.[99] Those two vaccines were developed by both the Beijing Institute of Biological Products Co., Ltd and the Wuhan Institute of Biological Products Co., Ltd. The clinical trials of those two vaccines revealed no safety concerns reported in the people who received those two vaccines.[99] The Sinovac Life Sciences, Beijing, China, developed an inactivated SARS-CoV-2 vaccine called CoronaVac.[100] Both phase I and II clinical trials for the CoronaVac revealed potential efficacy and safety in the vaccinated individuals.[100] Another recent study reported the encouraging trend of a new inactivated SARS-CoV-2 vaccine candidate prepared by the (PiCoVacc) company. They used the purified ten SARS-CoV -2 strains then inactivate them by beta-Propriolactone. This study showed this vaccine protects the non-human primates against the circulating strains of SARS-CoV-2.[97]

Some SARS-CoV-2 subunit vaccines

The subunit vaccines usually consist of purified antigens in the form of saccharides or conjugated proteins. They are generally prepared from viral synthetic peptides or recombinant proteins. The spike protein is the crucial player in viral pathogenesis, as well as the immune response. It is an ideal target for vaccine preparation using various strategies as well as diagnostic assays.[55,101] The DNA vaccine is much safer than other types of vaccines due to the absence of any microbial reversion and side effects. The key antigen in the subunit vaccine should be capable of inducing protective immune responses against a specific pathogen.[97] This vaccine candidate was used against SARS-CoV to stimulate a potent immune response against the spike proteins; as a result, neutralizing the binding site of viral protein and preventing its interaction with its specific receptor ACE2.[102] Some SARS-CoV-2 subunit vaccines are in the clinical stage, such as the vaccine developed by Queen's land University using Rapid Response Technology, the 'Molecular clamp' vaccine platform.[103] This technology can present the target vaccine straight forward to the immune system to induce a specific antibody response against the SARS-CoV-2.[103] Meanwhile, the

Clover Biopharmaceuticals is also working on developing a highly purified recombinant SARS-CoV-2-S protein subunit-trimer vaccine called (S-Trimer) through using their Trimer-Tag© technology.[104] Another example of the SARS-CoV-2 potential subunit vaccine is the immunogenic virus-like nanoparticles developed by Novavax Company. This type of vaccine is based on the expression of the recombinant SARS-CoV -2-S-protein. Moreover, the Texas Children's Hospital Center for Vaccine Development has developed another subunit vaccine against SARS-CoV-2 infection conjugated with alum, which incorporates the receptor-binding domain (RBD) of the viral spike protein.[105] Although most of these SARS-CoV -2 subunit vaccines are safe and elicit a specific immune response, they trigger low immunogenicity levels. Thus, to overcome this problem and to enhance the effectiveness of most subunit vaccines, immune response-enhancing adjuvant should be considered as in the case of using alum adjuvant above. Meanwhile, specific delivery systems must be convenient to have an optimal response.[106]

Some potential SARS-CoV-2 DNA vaccines

The DNA vaccine technology was well documented and had significant progress in the field of vaccinology of many pathogens, including some other coronaviruses.[107] Instead of having antigen substances in DNA – based vaccines, it is better to have a genetic component responsible for antigen production by the host. The DNA vaccines are mimicking natural viral infections. Both of them can trigger the antigen-presenting cells (APCs) to increase the expression of MHC-I as well as the intracellular mediated response via CD8 + T cells.[107] Furthermore, the antibody-mediated response was confirmed during the use of DNA vaccines.[107] To increase the efficacy of the DNA vaccines and to ensure a high delivery of them to the target cells, some components should be mixed with vaccines such as adjuvants, lipid complexes, and micro-particles.[108] Additionally, the INO-4800 (DNA vaccine) from *in ovo* has developed a vaccine using DNA plasmid encoding SARS-CoV-2-S protein delivered by electroporation. Shenzhen Geno-Immune Medical Institute has also been approved for phase I clinical trials for two vaccine candidates, LV-SMENP-DC and COVID-19 artificial antigen-presenting cells (APC). LV-SMENP-DC is composed of dendritic cells (DCs) modified with a lentiviral vector expressing synthetic mini-genes based on selected viral proteins to activate antigen-specific cytotoxic T cells.[88]

The emergence of new SARS-CoV-2 escape mutants and the fine-tuning of the vaccines and vaccination strategies

Several SARS-CoV-2 mutants were reported recently in many countries, especially the UK, South Africa, Brazil, and India.[109,110] These mutants have higher transmissibility and replication potential than the viruses reported in the early phase of the pandemic.[109,110] Most of these mutations occur

within the RBD of the S protein of the virus. These mutations enable the virus to bind firmly to its receptors; the ACE.[111] These mutants are posing significant risk to human health in many aspects. First, the high replication potentials make these mutants spread much faster in a certain population. Second, these mutants resulted in an increase in the number of hospitalization as well as the number of severe cases. This contributed to the high case fatality rates among the affected populations. Third, some of these mutants escaped the action of neutralizing antibodies generated because of both natural infections with older versions of the virus or antibodies from some vaccinated individuals with some of the recently deployed vaccines.[112] On the other hand, the new mutants may affect the sensitivity of the already developed diagnostic assays against SARS-CoV-2.[113] Several studies are recently showing that some of the mRNA-1273 vaccine-based SARS-CoV-2 vaccines may tolerate these escape mutations and are able to induce a potent reduction in the virus infectivity.[114] We believe the gold standard is the vaccination of the individuals against the homologous strains and variants of the virus is for achieving the required immune response; thus, protection against the natural infection may be granted. Careful and continuous monitoring of the virus is necessary at the current sage to prepare effective vaccines against the most recent circulating strains of the virus.

Conclusions

The host immune system is one of the key players in the battle against COVID-19. SARS-CoV2 adapts many unique evasion strategies to escape the effects of the host immune responses. The continuous emergence of new viral mutants making the virus several steps ahead of us in its control and mitigation. Through understanding various aspects of SARS-CoV/host immune system interaction, we may unrevealed some novel approaches for its control and prevention. Developments of various types of vaccines and immunotherapeutic are great steps toward the control of SARS-CoV-2. However, careful, and vigilant monitoring of the virus and its evasion strategies are necessary to contain SARS-CoV-2 and put an end to the current pandemic in the near future.

The virus enters the host cells after an interaction between the spike protein (S) and the ACE-2 host cell receptor in the presence of the TMPRSS2 ligands. The SASR-CoV-2 inhibits the early production of type-I Interferon, including IFN alpha, beta. The antigen-presenting cells (APC), such as macrophages that present antigenic peptides of the virus to the Th0 cells further lead to T cell activation and differentiation to different CD4 T cell subsets (i.e., Th1, Th2, and Th17). The Th1 produces various cytokines such as IFN-gamma, IL-2, and IL-12, which all can activate the CD8 T cells response. The Th2 cells exert their functions via the production of cytokines, including IL-4, IL-5, which activate the B-cell response and result in activation and differentiation into effector plasma cells and memory B cells. This can produce specific neutralizing antibodies against the common SARS-CoV-2 structural proteins, including (S, N, and M) proteins. The SARS-CoV-2 presented by macrophages in combination with MHC-1 will be recognized by CD8 T cells that can produce IFN-gamma, which plays an essential role in the process of viral clearance.

SARS-CoV-2 can infect the T cells (CD4 and CD8) and lead to a reduction in their total numbers. The pattern recognition receptors, including the Toll-like receptors, can recognize both the extracellular and the intracellular invaded pathogens. The TLR-4 expresses at the surface of airway epithelial cells, macrophages may also recognize the (s) protein, and once the virus releases its genomic RAN material into the cytoplasm during replication. The endoplasmic RNA sensors such as TLR-3, TLR-7, and TLR-8 can further recognize it; this may result in the induction of both the cytokines and the chemokines. Moreover, the infected host cells produce a wide range of pro-inflammatory cytokines and chemokines that also able to recruit several inflammatory cells at the site of infection. The level of their production is associated with the severity of the COVI-19 infection. Thus, the acute respiratory distress syndrome (ARDS) may lead in most cases to the death of the infected individuals; however, some patients may also recover. Red arrows showing inhibitory pathways, while the black arrows indicate an active pathway.

The virus enters the host cells after an interaction between the spike protein (S) and the ACE-2 host cell receptor in the presence of the TMPRSS2 ligands.[10] The SASR-570 inhibits the early production of type-I Interferon, including IFN alpha, beta.[115] The antigen-presenting cells (APC), such as macrophages that present antigenic peptides of the virus to the Th0 cells that are further lead to T cell activation and differentiation to different CD4 T cell subsets (i.e., Th1, Th2, and Th17).[116] The Th1 produces various cytokines such as IFN-gamma, IL-2, and IL-12, which all can activate the CD8 T cells response.[117] The Th2 cells exert their functions via the production of cytokines, including IL-4, IL-5, which activate the B-cell response and result in activation and differentiation into effector plasma cells and memory B cells.[112] This can produce specific neutralizing antibodies against the common SARS-CoV-2 structural proteins, including (S, N, and M) proteins. The SARS-CoV-2 presented by macrophages in combination with MHC-1 will be recognized 580 by CD8 T cells that can produce IFN-gamma, which plays an essential role in the process of viral clearance. SARS-CoV-2 can infect the T cells (CD4 and CD8) and lead to a reduction in their total numbers.[118] The pattern recognition receptors, including the Toll-like receptors, can recognize both the extracellular and the intracellular invaded pathogens. The TLR-4 expresses at the surface of airway epithelial cells, macrophages may recognize the (s) protein, and once the virus releases its genomic RAN material into the cytoplasm during replication.[119] The endoplasmic RNA sensors such as TLR-3, TLR-7, and TLR-8 can further recognize it;[120] this may result in the induction of both the cytokines and the chemokines. Moreover, the infected host cells produce a wide range of pro-inflammatory cytokines and chemokines that also able to recruit several inflammatory cells at the site of infection. The level of their production is associated with the severity of the COVI-19 infection. Thus, the acute respiratory distress syndrome (ARDS) may lead in most cases to the death of the infected individuals; however, some patients may also recover.[121] Red arrows showing inhibitory pathways, while the black arrows indicate an active pathway.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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