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A Brief Review on the Overview on Immunology of COVID-19: Current State of the Research

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Abstract: ***After the attack of Influenza(Flu) in1918 which later turned pandemic, the world is again facing a similar situation. Although, the advancement in medical science has made it possible to identify that the novel infectious agent is from the coronaviridae family. Rapid genome sequencing by various groups helped in identifying the structure and function of the virus, its immunogenicity in diverse populations, and potential preventive measures. Coronavirus attacks the respiratory system to be more specific it attacks ACE2 receptors, causing pneumonia and lymphopenia in maximum infected individuals. Viral subunits like spike and nucleocapsid proteins trigger an immune response in the host which eliminate the virus. These viral antigens can be either recognized by the B cells or by MHC complexes to the T-cells, resulting in antibody production, increased in cytokine secretion, and cytolytic activity in the acute phase of infection. Genetic polymorphism in MHC enables it to present some of the T-cell surface very well over the other MHC alleles. The association of MHC alleles and its down regulated expression has been correlated with disease severity against influenza and coronaviruses. Studies have reported that infected individuals can, after recovery, induce strong protective responses by generating a memory T-cell pool against SARS-CoV and MERS-CoV. These memory T-cells were not persistent in the long term and, upon reactivation, caused local damage due to cross-reactivity. So far, the reports suggest that SARS-CoV-2, which is highly contagious, shows related symptoms in three different stages and develops an exhaustive T-cell pool at higher loads of viral infection. As there are no specific treatments available for this novel coronavirus, numerous small molecular drugs that are being used for the treatment of diseases like SARS, MERS, HIV, ebola, malaria, and tuberculosis are being given to COVID-19 patients, and clinical trials for many such drugs have already begun. A classical immunotherapy of convalescent plasma transfusion from recovered patients has also been initiated for the neutralization of viremia in terminally ill COVID-19 patients. Due to various limitations of plasma transfusion, researchers are now focusing on developing neutralizing antibodies against virus particles along with immuno-modulation of cytokines like IL-6, Type-I interferons (IFNs), and TNF-α that could help in combating the infection. This review highlights the similarities of the coronaviruses that caused SARS and MERS to the novel SARS-CoV-2 in relation to pathogenicity and immunogenicity and also focuses on various treatment strategies that could be employed for curing COVID-19.***

Keywords: Immune response, interferons, toll-like receptors, innate immunity, placebo

1. Immune Sensing of SARS-CoV-2

Innate immune sensing serves as the first line of antiviral defense and is essential for immunity to viruses. To date, our understanding of the specific innate immune response to SARS-CoV-2 is extremely limited. However, the virus-host interactions involving SARS-CoV-2 are likely to recapitulate many of those involving other CoVs, given the shared sequence homology among CoVs and the conserved mechanisms of innate immune signaling. In the case of RNA viruses such as SARS-CoV-2, these pathways are initiated through the engagement of pattern recognition receptors (PRRs) by viral single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA) via cytosolic RIG-I like receptors (RLRs) and extracellular and endosomal Toll-like receptors (TLRs). Upon PRR activation, downstream signaling cascades trigger the secretion of cytokines. Among these, type I/III interferons (IFNs) are considered the most important for anti-viral defense, but other cytokines, such as proinflammatory tumor necrosis factor alpha (TNF-a), and interleukin-1 (IL-1), IL-6, and IL-18 are also released. Together, they induce antiviral programs in target cells and potentiate the adaptive immune response. If present early and properly localized, IFN-I can effectively limit CoV infection (Channappanavar et al., 2016, 2019). Early evidence demonstrated that SARS-CoV-2 is sensitive to IFN-I/III pretreatment in vitro, perhaps to a greater degree than SARS-CoV-1 (Blanco-Melo et al., 2020; Lokugamage et al., 2020; Mantlo et al., 2020; Stanifer et al., 2020). However, the specific IFN-stimulated genes (ISGs) that mediate these protective effects are still being elucidated. Lymphocyte antigen-6 complex locus E (LY6E) has been shown to interfere with SARS-CoV-2 spike (S) protein-mediated membrane fusion (Pfaender et al., 2020; Zhao et al., 2020c). Likely, the IFN induced transmembrane family (IFITM) proteins inhibit SARSCoV-2 entry, as demonstrated for SARS-CoV-1 (Huang et al., 2011), although their action in promoting infection has also been described for other CoVs (Zhao et al., 2014, 2018).

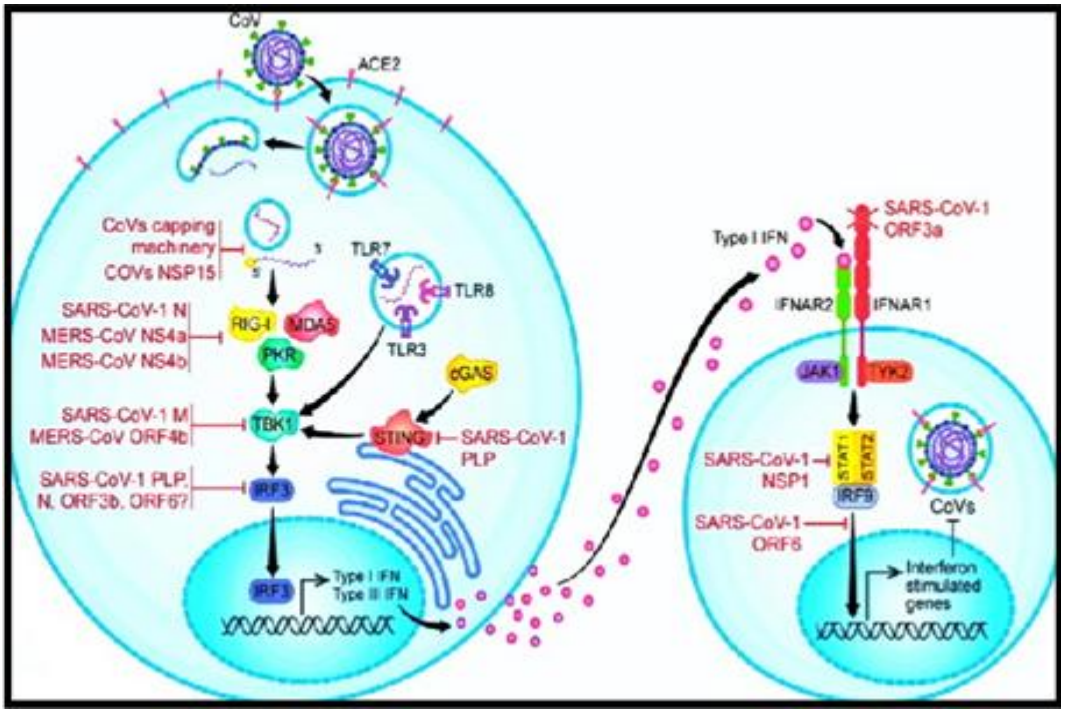

Figure1: Mechanisms of Host Innate Immune Response and Coronaviruses Antagonism: Overview of innate immune sensing (left) and interferon signaling (right), annotated with the known mechanisms by which SARS-CoV-1 and MERS-CoV antagonize the pathways (red)

2. Myeloid Cells Contribution to Pathogenic

Inflammation The initial mode of viral pathogen-associated signal (PAMP) recognition by innate cells has a major impact on downstream myeloid signaling and cytokine secretion (de Marcken et al., 2019). While macrophages are somewhat susceptible to MERS-CoV and SARS-CoV-1 infection (Perlman and Dandekar, 2005; Zhou et al., 2014), data do not suggest that they are infected by SARS-CoV-2, although one study reported ACE2 and SARS-CoV-2 nucleocapsid protein is expressed in lymph nodes and spleen-associated CD169+ macrophages of COVID-19 patients producing IL-6 (Chen et al., 2020h). Significantly elevated systemic levels of proinflammatory cytokine IL6 have been reported in several COVID-19 patient cohorts and shown to correlate with disease severity (Mehta et al., 2020). Increased IL-6 can also be associated with higher levels of IL2, IL-7, IFN-ɣ, and GM-CSF, as seen in secondary hemophagocytic lympho-histio cytosis. In response to viral infections, MNPs drive IL and IFN-I and IFN-III production resulting in inflammasome activation, induction of pathogenic Th1 and Th17 cell responses, recruitment of effector immune cells, and CRS pathology (Prokunina-Olsson et al., 2020; Tanaka et al., 2016). Independently, in vitro studies have demonstrated SARS-CoV1 infection can induce intracellular stress pathways, resulting in NLRP3-dependent inflammasome activation and macrophage pyroptosis (Chen et al., 2019; Shi et al., 2019). Functional studies are required to implicate these myeloid inflammasome pathways in COVID-19 lung pathology and to assess other immunogenic pathways such as RIPK1/3-dependent necroptosis (Nailwal and Chan, 2019). In conclusion, the strength and duration of myeloid ISG) signaling potentially dictate COVID-19 disease severity, but rigorous studies are warranted to confirm this. Lastly, more work is needed to ascertain the mechanistic role played by lung-resident and recruited granulocytes in SARSCoV-2 control and pathogenesis (Camp and Jonsson, 2017; Flores-Torres et al., 2019). In contrast to their early protective role, neutrophil NETosis and macrophage crosstalk can drive later-stage inflammatory cascades (Barnes et al., 2020), underscoring the overall pathogenic nature of damage-sensing host responses. Collectively, the current knowledge of CoVs and SARS-CoV-2 infection, in particular, points to an inadvertent collusion involving myeloid cells in COVID-19 pathogenesis, despite their critical role in early sensing and antiviral responses.

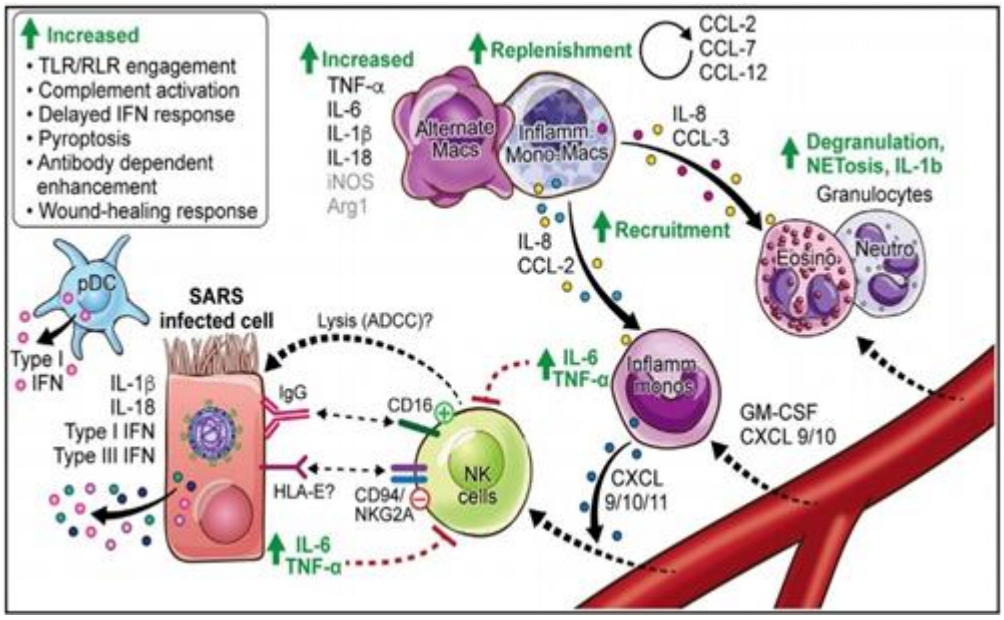

Figure2: SARS-CoV-2 Infection Results in Myeloid Cell Activation and Changes NK Cell Function

Based on data from preliminary COVID-19 studies and earlier studies in related coronaviruses. IL-6, IL-1b, and IFN-I/III from infected pulmonary epithelia can induce inflammatory programs in resident (alternate) macrophages while recruiting inflammatory monocytes, as well as granulocytes and lymphocytes from circulation. Sustained IL-6 and TNF-α by incoming monocytes can drive several hyperinflammation cascades. Inflammatory monocyte-derived macrophages can amplify dysfunctional responses in various ways (listed in top-left corner). The systemic CRS- and sHLH-like inflammatory response can induce neutrophilic NETosis and microthrombosis, aggravating COVID-19 severity. Other myeloid cells, such as pDCs, are purported to have an IFN-dependent role in viral control. Monocyte-derived CXCL9/10/ 11 might recruit NK cells from blood. Preliminary data suggest that the antiviral function of these NK cells might be regulated through crosstalk with SARS-infected cells and inflammatory monocytes. Dashed lines indicate pathways to be confirmed. Arg1, arginase 1; iNOS, inducible-nitric oxide synthase; Inflamm., inflammatory; Mono., monocytes; Macs, macrophages; Eosino, eosinophils; Neutro, neutrophils; NETosis, neutrophil extracellular trap cell death; SHLH, secondary hemophagocytic lymphohistiocytosis.

T Cell Responses

T cells play a fundamental role in viral infections: CD4 T cells provide B cell help for antibody production and orchestrate the response of other immune cells, whereas CD8 T cells kill infected cells to reduce the viral burden. However, dysregulated T cell responses can result in immune-pathology. To better understand the role of T cell responses in SARS-CoV-2 infection, the pursuit of two major questions is imperative: (1) what is the contribution of T cells to initial virus control and tissue damage in the context of COVID-19, and (2) how do memory T cells established thereafter contribute to protective immunity upon reinfection? Some tentative answers are beginning to emerge.

3. Replication

All coronaviruses initiate entry inside the target cell by engaging the host receptor with the S glycoprotein present on their surface so as to gain entry inside the target cell. The region of S protein containing the RBD is present on the S1 subunit. In a few coronaviruses, RBD is present at the N-terminus region of S whereas in SARS-CoV, it is situated at the C-terminus region. The fusogenic activity of virus cell membrane is governed by two tandem domains, heptad repeats (HR1,2) that are present on the S2 region of S protein (30, 31). Initially, it was believed that SARS-CoV enters the target cell merely by virtue of cell membrane integration of virus particle and host cell membrane. Later, it was discovered that an essential proteolytic cleavage event takes place in the S protein at the S2 position of SARS-CoV that results in membrane fusion and facilitates virus entry inside the cell. Once the coronavirus is inside the host cell via membrane fusion, it releases its +ve ssRNA genome into the cytoplasmic compartment, where the translation of ORF-1a and ORF-1b begins resulting in the formation of two large polyproteins (pp1a and pp1ab). Three functional proteases then cleave the polyproteins into 16 non-structural proteins (NSP1-16), which eventually create the viral RNA polymerase and other accessory proteins for virus assembly. An uninterrupted replication-transcription event results in the formation of various nested sets of subgenomic (sg) mRNAs that eventually translate into numerous structural and accessory proteins. The E glycoproteins after synthesis are incorporated into therough endoplasmic reticulum or Golgi membrane. The +ve RNA combines with capsid protein to form the nucleocapsid, followed by budding of assembled virus particles in the ERGolgi Intermediate Compartment (ERGIC). Lastly, the virus particle-loaded vesicles are fused with the cell membrane for effective shedding of the virus. These new virions are now accessible to infect the neighboring healthy cells and are also released into the surrounding environment via respiratory droplets that are highly contagious and hence potentially spread the disease to healthy individuals.

Pathogenesis of COVID-19:

The path followed by SARS-CoV-2 to reach the lungs is via the naso-oral cavity. Once the virus is inhaled, it enters the epithelial cells of the nasal cavity by engagement of ACE2 receptor with the viral RBD and initiates its replication. This initial asymptomatic phase lasts for about 1–2 days, during which the virus multiplies in the upper respiratory tract, where no major hindrance is caused by the innate immune cells. Within 2–14 days of initial encounter, the common symptoms of COVID-19 start to appear, which are similar to those of SARS and MERS, i.e., fever, dry cough, pharyngitis, shortness of breath, joint pain, and tiredness. Numerous problems arise during this phase of the disease, including nosocomial and fomite transmission of infection, which enhances the chances of community spread. Soon, the virus begins to move toward the lower respiratory tract via airways, and this triggers a strong innate immune response. Patients at this stage start exhibiting enhanced pro-inflammatory response that leads to viral sepsis accompanied by other complications, including pulmonary edema, Acute Respiratory Distress Syndrome (ARDS), different organ failures, and death in the worst scenarios. The infected individuals rarely show the intestinal symptoms like diarrhea that were evident in other coronavirus infections. Patients are recommended to be quarantined to prevent community spread of this pandemic virus. The severity of COVID-19 has been found to be greater in aged individuals and in people with a health history, such as those immune-compromised by HIV infection or by chemotherapy for cancer. Diabetic and asthma patients, along with individuals with hypertension, obesity, or heart, kidney, or liver disorders, are also at higher risk if they acquire the disease. Autopsy reports of individuals who died due to SARS show multi-organ dysfunction, with the highest viral titers in the lungs and immune cells in circulation, thus damaging the pulmonary and immune system. As opposed to adults, only a very small population of children has been infected with SARS-CoV-2. In one study, the symptoms displayed by children above 15 years were found to be milder as compared to those of younger children, who showed severe symptoms but with rare deaths and better prognosis. The study speculated two major possibilities related to COVID-19 severity in children among different age groups. One of these rests on the finding that ACE2 activity is higher in children aged 4–13 years; after this age, it starts to decline until adolescence. This could be one of the reasons why lung fibrosis is observed mainly in younger children.

Pathogenicity of COVID-19:

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Secondly, deferential CD4+ and CD8+ T cell populations have been seen in children as compared to adults. A large number of clinical and epidemiological criteria were defined to assess probable pediatric cases of COVID-19. A preliminary report from a cross-sectional study of children admitted to US and Canadian Pediatric Intensive Care Units (PICUs) during March 14-April 3, 2020, revealed that the 48 children were admitted in the USA whereas no COVID-19 cases were reported in Canadian PICUs. The study revealed that there are fewer COVID-19 cases in children as compared to adults and that there is a median PICU time of 5 days. A recent preprint from Paris reports that 11 children (age 3.7–16.6) were admitted experiencing symptoms similar to Kawasaki disease (KD) along with gastrointestinal issues and elevated inflammatory markers. Further investigation suggested that they were also SARS-CoV2-positive, speculating that this could be the reason for KD shock syndrome. Similar cases have been observed in New York, where four otherwise healthy SARS-CoV-2-positive children started displaying symptoms similar to KD and toxic shock syndrome, thereby needing intensive care. Therefore, medical practitioners should be prepared to tackle such sudden post-infection complications to avoid the associated risks.

4. Treatment strategies for COVID-19:

Just like SARS and MERS, there are no specific clinically approved drugs available for COVID-19. Currently, the treatment regime focuses mainly on providing intensive care in order to alleviate the symptoms and discomfort associated with COVID-19. Conservative fluid therapy accompanied by broad-spectrum antibiotics are also given to the patients as a protective measure to avoid opportunistic bacterial infections. However, ventilator support for respiration is provided to the patient under extreme conditions. Numerous FDA-approved antiviral drugs, vaccines, and immune-therapies that are already being used to treat other diseases have also been considered as a possible approach for treating COVID-19. But this approach may reduce the availability of these drugs and vaccines for the intended diseases and for the patients with the greatest need. The molecular, structural, and functional relationships of SARS-CoV-2 with SARS-CoV might define the use of existing anti-viral drugs against COVID-19, considering the total time it takes to perform clinical trials and get FDA approval for the use of novel drugs and vaccines. The increasing knowledge of the genetic, immunological, and molecular mechanisms behind its enhanced pathogenicity might help in developing specific treatment approaches for COVID-19 in the future.

Antiviral Agents

Considering the studies on the molecular mechanism of coronavirus infection, several antiviral drugs could be repurposed for the treatment of COVID-19. Remdesivir is a nucleotide analog that acts as an antiviral agent for a wide variety of viruses and has been tested widely against previous epidemics of coronavirus infections in both in-vitro and in-vivo models. This adenosine analog gets incorporated into the newly synthesized viral RNA, which inhibits the addition of further nucleotides by viral RNA-dependent RNA polymerase and hence terminates the ongoing transcription. Administration of intravenous remdesivir was found to be effective in treating the first known patient of COVID-19 in the USA. A randomized double-blinded clinical trial on 1,059 adult hospitalized COVID-19 patients was sponsored by the National Institute of Allergy and Infectious Diseases, USA, to further test the potency of intravenously administered remdesivir. The preliminary outcomes of the trial reported that remdesivir treatment decreased the median recovery time in the treatment group (11 days) as compared to the placebo group (15 days). The mortality rate was also less in the treatment group (7.1%) in contrast to the placebo group (11.9%). Numerous clinical studies, similar to this, are required so as to validate the proposed drugs for COVID19. Favipiravir, ribavirin, and galidesivir are also potential nucleoside analogs that might be useful against novel coronavirus infection. The combinatorial therapy approach of using remdesivir along with chloroquine, a well-known anti-malarial drug, has also been tested in vitro so as to study its effectiveness against SARS-CoV-2. It has been reported that chloroquine immuno-modulates the host micro-environment and also interferes with the replication of the virus and its interaction with the receptor. In a randomized clinical trial (NCT04308668) involving 821 asymptomatic individuals across the US and Canada who had come into close contact with potential COVID-19 patients, the individuals were given either hydroxyl chloroquine or placebo as a prophylactic measure. The results revealed that hydroxy chloroquine treatment had the same effect as did the placebo group. The usage of hydroxyl chloroquine resulted in minor side effects (40.1%) as compared to the placebo treatment (6.8%). However, no cardiovascular disorder or treatment-related major complications were observed. Based on the putative function of hydroxyl chloroquine on the endosomal acidification, whereby it is presumed to hinder viral uncapping, it can be observed that it has a great potential for prophylaxis, not to prevent infection but to reduce effective viral load in patients and thus lead to milder disease. Numerous clinical trials to further explore the usage of hydroxyl chloroquine in different combinations are in the pipeline and will finally provide a better understanding of the efficacy of this drug for COVID-19. A few anti-HIV drugs, such as lopinavir/ritonavir in combination with interferon beta (IFN-β), have been tested in vivo for treating coronavirus infections(SARS-CoV, MERS-CoV) and have also been used in the case of COVID-19. Various complementary therapies could also be employed as a preventive measure against viral infections. Many essential proteases, such as chymotrypsin (3C-like protease) and PLpro, which are required by coronavirus for completing the replication process, can also be targeted using drugs. Cinanserin, flavonoids, and some small molecules are known to inhibit 3CLpro, whereas diarylheptanoids are used to inhibit PLpro. In a recent study, 16 potential anti-HCoV drugs were identified through a systems biology-based approach, such as melatonin, mercaptopurine, sirolimus, dactiomycin, and toremifene, which are to be tested further for their potency.

Convalescent Plasma Therapy:

In the absence of any dependable vaccine or drugs with tested efficacy and when the pandemic onslaught is ongoing, a worthy therapeutic approach is passive immunization using purified antibodies. The source of such antibodies could be the sera of convalescing individuals, mAbs, or genetically modified antibodies from an animal host, which can efficiently neutralize the virus. This is an age-old practice, with pioneering work having been done by the Nobel Laureate, Emil Behring, who applied this approach for diphtheria, and has been used whenever there are sudden outbreaks of viral diseases like SARS, MERS, H1N1, H5N1, Ebola, and many others. As opposed to active vaccination, plasma therapy is the only means to provide immediate immunity for viral clearance, as in the case of SARS-CoV-2. As in other epidemic diseases, convalescent sera are currently being employed for COVID-19 in a number of countries. Although a randomized controlled trial is yet to be reported, limited studies in 10 patients have been documented with no remission of severe respiratory afflictions on receiving neutralizing antibodies from 39 convalesced donors with antibody titers of 1:160, along with drugs and oxygen support. A report from Hong Kong suggested that this therapy had poor outcome in SARS patients, with a number of limitations in their study. As with transfusion of any blood products, precautionary screening of infectious agent is warranted in plasma transfusion. Recently, the FDA in the USA has approved trials of convalescent plasma therapy in COVID-19 under specific guidelines; plasma donation is advised 3 weeks after a

patient becomes virus-negative on PCR. The major challenge in this therapy is obtaining donors with similar blood antigens with a high antibody titer of SARS-CoV-2. Another potential adverse effect of this approach is ADE of infection, which is common in so many other viruses. But, to date, the incidence of ADE has not been reported in the case of SARS-CoV-2. Another major point of contention is the selection of patients for this therapeutic approach. In most clinical trials, patients with severe diseases are being recruited, while the presumed mechanism of action of convalescent plasma, based on its content of virus-neutralizing antibodies, rather points to plausible favorable outcomes in earlier phases of the disease because in the later, more severe phases, the hyper-immune response, rather than the viral load, becomes the more critical pathology. Finally, there are no available data on the heterogeneity of response to convalescent plasma transfusion, which may further illustrate the importance of careful evidence based patient selection, as heterogeneity of response may result from both virus and host intrinsic factors which are not yet revealed.

Vaccine Design Strategies

Researchers around the world are working hard to develop a potential vaccine candidate so as to stop the deadly pandemic caused by SARS-CoV-2. However, vaccine development is not an easy task, as a number of successful clinical trials are required before approval for patients. Different approaches are being utilized for designing a specific vaccine targeting either the structural proteins or viral replication process, which eventually results in the inhibition of viral growth and its further transmission. The common strategies involve the use of live attenuated vaccine (LAV), inactivated virus, subunit vaccines, monoclonal antibody vaccine, virus vectors, protein vaccines, and DNA/RNA-based vaccines. There are numerous subunit vaccines targeting all or a part of S protein that have already been tested for SARS and MERS in animal models and could be potential candidates for testing against SARS-CoV-2. A recent pilot study with a purified inactivated SARS-CoV-2 virus vaccine displayed very promising outcomes in different animal models. The neutralizing antibodies generated after vaccination were able to effectively target 10 different strains of SARS-CoV-2 without developing any ADE of infection. Various randomized controlled trials (NCT04327206, NCT04328441) are also underway to evaluate the effectiveness of the BCG vaccine against SARS-CoV-2 for healthcare professionals. An adenovirus vector-based vaccine candidate, ChAdOx1 (presently AZD1222), developed by Oxford University (licensed to Astra Zeneca) against SARS-CoV-2 has been reported to activate both the humoral and cell-mediated immune response when tested in rhesus monkey. The phase I clinical trial to confirm its potency is also in progress (NCT04324606). Another group has followed a similar approach by using a recombinant adenovirus type 5 (Ad5-nCoV) vector based vaccine for COVID-19. The full report from the phase I clinical trial (NCT04313127) of Ad5-nCoV shows that it is very effective in generating both humoral and rapid T-cell response post immunization. The group is now ready for the next clinical trial phase to further strengthen the effectiveness of the Ad5nCoV vaccine. It should be noted that there are potential risks associated with the usage of live attenuated viruses, for example, complications resulting in lung damage by infiltrating eosinophils, as seen in in vivo models. However, eosinophil immune-pathology due to SARS-CoV vaccine could be reduced by using TLR4 agonist as an adjuvant. Viral neutralizing antibodies specifically targeting various regions of S, i.e., S1-RBD, S1-NTD, or the S2 region, and blocking the interaction of virus with the receptor are well-known for SARS and MERS. These neutralizing antibodies could prove to be the best and potential candidate for cross-neutralization of SARS-CoV-2. Despite being structurally related, some of the SARS-CoV neutralizing monoclonal antibodies failed to interact with the S-protein of SARS-CoV-2, which could be attributable to the substantial differences in their RBD. A recent study reported the presence of high titres of neutralizing antiS-RBD IgG antibodies, but no antibodies were detected against the N protein in recovered COVID-19 patients, suggesting that anti-S IgG persists longer than does anti-N IgG. Along with the humoral immune response, they also observed an S protein-specific T cell-population producing IFN-γ, which further contributes to conferring protective immunity against SARS-CoV-2 infection. Recently, a monoclonal antibody (47D11) has been identified from 51 SARS-Spike hybridomas that targets the conserved S-RBD region and can very effectively neutralize SARS-CoV-2 along with SARS-CoV. On similar lines, a group has isolated a single-domain antibody from a phage display library targeting the S-RBD region of SARS-CoV-2. The fully humanized single domain antibody was able to neutralize the virus by interacting with a cryptic epitope in S protein. These mAb and single domain antibodies could be used to treat as well as to design quick diagnostic kits for COVID-19. The new technology of the micro-needle array(MNA)has been employed for delivering SARS-CoV-2 S1 subunit vaccine, which could be really helpful in the treatment of the emerging COVID19 outbreak. The transfer of S1 subunit by MNA elicited a strong virus specific-antibody response in SARS-CoV-2. A novel encapsulated mRNA vaccine candidate developed by ModernaTX, Inc. that encodes full length S protein of SARSCoV-2, is also under clinical trial (NCT04283461). There is an urgent need to develop more such specific vaccines that could neutralize the novel coronavirus effectively.

Immunomodulatory Therapies

The host innate immune system encounter supcoming infections, and this results in elevated production of various cytokines and type-I interferons (IFNs). In the case of prolonged infection, hyperactivation of the immune system may also result in the development of a pro-inflammatory microenvironment, leading to adverse outcomes and even death. The induction of numerous lymphokines, such as IL-6, IL-1β, TNF-α, and CCL2, that are pro-inflammatory in nature has also been observed in the case of COVID-19. A previous study in a MERS animal model showed that treatment with recombinant type-1 IFN(rIFN) decreased the viral RNA level in lungs with a decrease in IFN-stimulating gene expression. Early treatment with rIFN resulted in a dampening of cytokine and chemokine release that lowered the migration of neutrophils and other cells in lung. An allogenic mesenchymal stem cell-based (RemestemcelL) therapy developed by Mesoblast, which has been previously

used for inflammatory conditions and graft vs. host disease in children and adults, is now being assessed for COVID19 . In this therapy, bone marrow derived MSCs from the donor are grown in vitro and are then transfused to the recipient patients. Upon infusion, these cells exhibit anti-inflammatory activity by reducing pro-inflammatory cytokine production via the recruitment of anti-inflammatory cells in the affected tissue. Currently, arandomized placebo-controlled trial (NCT04371393) with 300 patients is ongoing for treating ARDS caused by COVID-19. Treatment with rIFN, inhibitors of the pro-inflammatory pathway, cytokine inhibitors such as tocilizumab, lenzilumab, and many others are still to be used in combination with other drugs for treating COVID-19. So far, there is not much evidence from clinical trials of such inhibitors with which to predict the outcome of these anticytokine therapies.

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