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Review Article

The cross-talk study between immune system and SARS-CoV-2

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ABSTRACT

The emergence of SARS-CoV-2 driven by natural selection along with an aleatory event of genetic drift has marked the third introduction of a notorious and highly pathogenic entity into the human world. Since its initial identification in December 2019, the virus has overwhelmed the lives of millions while threatening billions around the globe. Although most of the infected individuals suffer from common and mild symptoms, for instance, cough and fever accompanied by a good prognosis. The disease can worsen into life-threatening cases of pneumonia and even multisystem failure. The documented studies for the case in view i.e., SARS-CoV-2 have highlighted the concurrent and coordinated involvement of all the components of the defense system which in turn determine the elimination of the virus followed by the convalescence from the diseased phase. This review is intended to provide a comprehensive overview of the existing knowledge concerning the immune response induced by SARS-CoV-2, the immediate mediators involved, and the long-term response. Several immune components contribute to disease severity and or recovery. Therefore, understanding the immune response to the virus is critical to improving the treatment and management of COVID-19.

Keywords: COVID-19, SARS-CoV-2, Immune system, Immunity

Introduction

The novel coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a devastating global pandemic of recent times [1, 2]. The disease has impacted nearly every corner of the globe, claiming the lives of nearly 6,879,677 and affecting over 761,071,826 individuals leading to societal instability [3]. As the name implies, the SARS-CoV-2 virus belongs to a well-known group of Coronaviruses [4, 5]. Taxonomically, Coronaviruses are members of the order "Nidovirales" and the family of Coronaviridae [6, 7]. Recent classification has distinguished these viral entities into four distinct genera namely, Alpha (α), Beta (β), Gamma (γ), and Delta (δ) Coronaviruses (CoVs) [8, 9]. Upon rigorous genomic analysis, the striking similarity between the culprit of the recent pandemic and SARS-CoV-1 led the Coronaviridae Study Group (CSG), a working group of the International Committee on Taxonomy of Viruses (ICTV) to place SARS-CoV-2 under the β-CoVs, thereby highlighting the intriguing genetic relatedness existing between these viruses.

Formerly, major outbreaks caused by SARS-CoV (2003) and MERS-CoV (2013) resulted in devastating consequences [10]. Although most of the infected individuals suffer from mild disease experiencing cough and fever with recovery within a few days, providing adequate medical care, the disease can worsen into life-threatening pneumonia-like illness, acute respiratory and/or multisystem arrest along with coagulation episodes. The interplay between the host's immune system and SARS-CoV-2 is an intricate process involving several chemical mediators, cells, and tissue. Understanding the immune response to SARS-CoV-2 remains a critical area of investigation to date. In this regard, the present review article is aimed to provide a comprehensive understanding of the immune response triggered by SARS-CoV-2, focusing both on the "innate" and "adaptive" arms of the immune system and exploring the immediate mediators involved. It is followed by a discussion on the pathological implications of the exaggerated immune response and the

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associated progression of the disease. Before we dive into the intricacies of the main subject of the review, At first the review will provide a summary of the life cycle of SARS-CoV-2, thereby better comprehending the succeeding content concerning the defense mechanism.

Transmission, life cycle, and replication of SARS-CoV-2

Initially, during the nascent stages of the outbreak, the disease was presumed to be of entirely a zoonotic origin, while the respiratory droplets were the major source of the transmission. Nevertheless, mounting evidence and extensive research shed light on the additional modes including direct human-to-human transmission and vertical transmission. In essence, successful infections require the delivery of replication-competent viral particles to the susceptible anatomical sites of the host [11]. The initial entrance of virus particles is triggered by the binding of the receptor binding domain (RBD) from the S protein to the surface receptors of human host cells. The angiotensin-converting enzyme 2 (ACE2), is proposed as one of the pivotal docking sites for SARS-CoV-2 which is ubiquitously distributed among several organs such as the intestine, kidneys, liver, lungs, heart, and vascular endothelium along with others. The other subordinate receptors facilitating the infiltration of viruses have also been documented [11]. After the establishment of interaction with RBD, the S protein then undergoes a series of proteolytic cleavage catalyzed by numerous proteases from the host including TMPRSS2, furin, and cathepsin B/L. Afterward, there is a fusion of the host and viral membrane and the subsequent release of viral RNA into the host's cytoplasmic milieu. The successful translation utilizing the cellular machinery yields polyproteins, pp1a and pp1b which upon autoproteolytic processing are processed into a total of sixteen NSPs. The NSPs in turn form a a replicase-transcriptase complex (RTC), remodeling the membrane and favoring the synthesis and replication of viral RNA. In particular, the process of replication and transcription occurs in the endoplasmic reticulum (ER) derived double-membrane vesicles (DMVs). The intrinsic pore channels export the newly generated genomic material from the interior of the DMV which is then encased in N protein. The structural proteins i.e., S, E, M, and N along with other accessory proteins are translated from sub-genomic RNAs (sgRNAs). The anchored core proteins (S, E, and M) from the ER membrane migrate to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC), an assembly site for the virion. Once formed, the complexes of viral ribonucleoproteins (vRNP) traverse towards the ERGIC, and undergo envelopment formation, followed by budding in the lumen. Lysosomes then finally facilitate the exocytosis of the enveloped virion [11].

Clinical spectrum of COVID-19

SARS-CoV-2 follows a typical incubation period ranging from 1–14 days, with 5 days being the most probable time. Although any individual is susceptible to SARS-CoV-2 infection irrespective of age, the symptomatic profile can be different. The infection in some cases is asymptomatic, while in others may present with critical illness [11]. The clinical spectrum in turn can be broadly described into two phases:1) a viral response phase comprising the incubation period, the initial infection followed by the pulmonary phase, and 2) the host's overzealous inflammatory phase. A progressive decline in the viral loads is postulated to correspond with the mentioned clinical stages, followed by a gradual intensification in the inflammatory response. Severely ill patients are predisposed to the development of metabolic acidosis, coagulopathy, septic shock, and ARDS. Furthermore, such cases are likely to suffer from the impairment of multiple vital organs, for instance, the heart and kidneys, hence proved to be challenging in terms of resolution. The exaggerated immune response is proposed as the prime determinant of the disease severity rather than the cytopathic effect induced by the disease agent. Most COVID-19 patients suffer from mild to moderate disease [12].

Immune response during SARS-CoV-2 infection

Innate immune response; the frontline of clearance in COVID-19

Cells of innate immunity such as monocytes, macrophages, neutrophils, dendritic cells (DCs), and natural killer (NK) cells, are armed with diverse arrays of pathogen recognition receptors (PRRs), recognizing DAMPs or pathogen-associated molecular patterns (PAMPs) to stimulate inflammatory pathways, evoking immune response. Since the entrance of the virus is facilitated by the S protein, the viral RNA along with the S protein is considered as prime PAMPs mediating the immune signaling events. The retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), Toll-like receptors (TLRs), C-type lectin receptors nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), are some of the well-known PRRs [13]. Upon activation, these receptors trigger downstream signaling of multiple pathways which ultimately lead to the secretion of Type I and III interferons (INF). Additionally, assembly and activation of different inflammasome complexes i.e., NOD-like receptors facilitate the release of pro-inflammatory cytokines [13].

SARS-CoV-2 and pathogen recognition receptors (PRRs)

TLRs, integral membrane PRRs upon PAMP recognition, dimerize and recruit the adaptor proteins namely MyD88 or TRIF [14]. These adaptor proteins activate nuclear factor kappa B (NF-κB) and MAP kinases which via a cascade of events may result in transcribing some proinflammatory genes such as tumor necrosis factor (TNF), IL-1, and IL-6. Further, TLRs promote the nuclear translocation of IRF-3 and IRF-7; the transcription factors thereby stimulating the expression of type I-IFN and IFN-stimulated genes (ISG) [15]. On the other hand,

RLRs include RIG-I, MDA5, and LGP2 sense the single-stranded RNA of SARS-CoV-2. In mitochondria, MDA5 and RIG-I interact with the mitochondrial antiviral signaling (MAVS), which results in the formation of the MAVS signalosome. This complex activates several factors, facilitating its nuclear translocation and transcription of genes involving type I and III, IFNs [15]. However**,** NLRs are reported to induce the production of pro-inflammatory cytokines and type I IFNs. When triggered, NLRs lead to the release of IL-1β and IL-18, activation of caspase-1, and gasdermin (GSDM) D's cleavage, responsible for membrane rupture. Increased plasma levels of IL-1β and IL-18 were correlated with critical conditions and fatality in COVID-19 patients [15].

Cells of the innate immune system and SARS-CoV-2

Macrophages; the phagocytic cells

The mononuclear phagocytes: monocytes and macrophages are the major drivers in the recruitment of leucocytes and regulation of inflammation. A mounting body of evidence suggested disturbances in the frequency of monocytes in SARS-CoV-2 infection. An alveolar mice model demonstrated the expression of ACE-2, TMPRSS2, and furin, suggesting their potential as possible target cells by SARS-CoV-2 [16]. At the onset of the infection, the structural proteins of SARS-CoV-2 are sensed by the TLR present on the surface of macrophages, inducing M1 polarization [17]. Severe infection triggers different phenotypical and morphological changes, particularly, a heightened monocyte-macrophage activation from an anti-inflammatory state, characterized by a mixed population (M1/M2), upregulation of CD206 and CD80 along with the secretion of multiple cytokines (TNF-α, IL-6, IL-10). In support of this, Karwaciak and coworkers also documented increased levels of IL-6 from monocytes and macrophages when cultured in the presence of S and N proteins of SARS-CoV-2 [18]. A significant decrease in $CD16^+$ and a shift toward $CD14^+$ monocytes were observed in severe cases of COVID-19 [19]. The expression of human leukocyte antigen (HLA) on monocytes and macrophages is also documented to be affected by SARS-CoV-2. Severe COVID-19 cases demonstrated low expression of HLA class II specifically, HLA-DR on monocytes when compared with non-critical cases [19]. This decrease signifies an immune suppressed state where patients were unable to produce efficient T cell response. The precise mechanism of proinflammatory response elicited by peripheral monocytes is uncertain yet. An attempt by Liao and colleagues suggested trafficking to lungs followed by differentiation into macrophages and the secretion of proinflammatory mediators that recruit other components of innate immunity [20].

Dendritic cells (DCs); the bridging component

DCs serve as a bridge linking "innate" and "adaptive immunity" with documented roles in shielding the host against SARS-CoV-2 infection. PRRs expressed on the DCs' membrane which upon activation can induce a range of signaling pathways. NF-kB, interferon regulatory factor 7 (IRF7), and IRF3 regulate some proinflammatory cytokines like IL-6, TNF-α, MIP-1α and 1β, monocyte chemoattractant-1 among many others. Many of the products released by SARS-CoV-2 may induce pyroptosis, recruiting DCs and other immune cells to infiltrate lung tissues. This in turn also promotes the secretion of multiple cytokines specifically, IL-1b, IL-6, IL-10, IL-17, TNF, GM-CSF, IFN-induced protein 10, and monocyte chemoattractant-3 [21]. DCs can ingest foreign particles, which are involved in processing and presenting antigens to lymphocytes. DC-specific intracellular adhesion molecule-grabbing nonintegrin (DC-SIGN) seems to serve as an attachment factor for SARS-CoV. Further, the interaction of CD147 and S protein has been described as a novel route for viral entry [22]. It is important to mention here that CD147 is found expressed by DCs, thus corroborating the chances of DCs infection by SARS-CoV-2. Recent findings suggested depletion of conventional DCs ($CD11c^+$) in patients with acute SARS-CoV-2 infection compared to those in the convalescent phase [23]. Since DCs are a critical determinant of the immune response against viruses, it is expected that viruses would have developed ways to target these cells and/or interfere with their functions.

Natural killer (NK) cells

NK cells are among the central players during viral infection. These cells owing to the presence of killer-cell immunoglobulin-like receptors (KIR) and CD16A are responsible for the direct killing effect of virally infected cells as well as exhibit antibody-dependent cellular cytotoxicity, respectively. Via active cross-talk with dendritic cells, NK cells play a significant role in antigen presentation and thus in adaptive immune response. The activation of NK cells induces the release of pore-producing enzymes like perforin and granzyme, directly denaturing the infected cells. Furthermore, the expression of executioner molecules i.e., TNF-related apoptosis-inducing ligand (TRAIL) and FAS ligand (FasL) is responsible for the initiation of extrinsic apoptotic pathway against the targeted cells [24]. NK cells are a major source of chemokines as well as pro-inflammatory cytokines including IFN- γ, TNF-α, and GM-CSF. Recent findings reported a low number of lymphocytes and NK cells in SARS-CoV-2-infected patients [25]. Furthermore, substantial depletion of NK cells is found to be related to the severity of the disease compared to non-severe cases. Initially, the reduction was attributed to the trafficking of NK cells to the lungs, since reported studies from COVID-19 patients indicated an increased number of NK cells in bronchoalveolar lavage (BAL) fluid [20]. However, by utilizing samples from similar sites, Demaria and coworkers documented decreased levels of NK cells ($CD16^+$, $CD56^+$, $CD57^+$) in patients with ARDS further endorsing that the depleted levels in blood are not a result of any migratory event [26]. Due to the loss of NK cells in COVID-19 patients,

and the low risk of graft-versus-host disease (GVHD), infusing ex-vivo expanded NK cells provides off-shelf anti-viral therapy to reinstate immune capacity and enhance recovery. In pursuit of this few, ongoing clinical trials are registered on Clinicaltrials.gov including NK cell infusion from hematopoietic stem cells (NCT04365101), NK cells plus standard therapy (NCT04280224), IL-15 super agonist and GM-CSF neutralizing, scFv-secreting NKG2D-ACE2 CAR-NK cell therapy (NCT04324996) [27].

Soluble mediators of the innate immunity and SARS-CoV-2

The cytokine connection

Cytokines, the small soluble proteins weighing less than 40kDa, are critical for normal homeostasis and are also implicated in various pathologies. Cytokines regulate immune and inflammatory responses via intricate networks, serving as valuable clinical indicators for many ailments. Documented literature suggested a positive correlation between COVID-19 disease progression and dysregulated cytokine profiles. Increased levels of IL-1Ra, IL-1β, IL-7, 8, 9, and 10, GCSF, FGF, GM-CSF, CCL2, 3, 4, CXCL10, PDGF, VEGF, and TNF-α have been observed in COVID-19 patients compared with healthy controls. When compared with non-ICU cases of COVID-19, the ones in intensive care had elevated levels of IL-2, 7, and 10, GCSF, CCL2, 3, CXCL10, and TNF-α. In support of this, similar findings have been reported in a USA cohort by Blanco-Melo and coworkers where increased levels of various cytokines and chemokines were observed in SARS-CoV-2 [28]. The role of IL-1 in driving COVID-19 pathogenesis has also been highlighted by Ong and colleagues. The transcriptional analysis carried out on severe COVID-19 patients' whole blood unveiled the upregulation of IL-1A and β during respiratory distress, while elevated levels of IL-6 were observed following respiratory improvement [29]. It is worth mentioning here that the levels of several proinflammatory cytokines were not markedly elevated in mild cases, indicating an exaggerated secretion of inflammatory mediators as a characteristic feature of severe COVID-19 [29]. The local cytokine response in bronchoalveolar lavage fluid (BALF) revealed upregulation of chemokine signaling, with a significant upregulation of CXCL17, CXCL8, CCL2, IL1β, and IL1RN. In connection with this, Xiong and coworkers highlighted the association of excessive release of cytokines for instance CXCL10/IP-10, CCL2/MCP-1, CCL3/MIP-1A, and CCL4/MIP1B to the COVID-19 pathogenesis [30]. The multiorgan impairment or failure can be well linked to cytokine stress and the resultant inflammation-driven cell death since ARDS and lung damage have been seen in several severely-ill COVID-19 patients. In light of this, a mounting body of evidence highlighted that the structural damage incurred by the membranes of endothelial cells is coupled with vascular leakage which plays a central role in the initiation and further propagation of ARDS during SARS-CoV-2 infection [31]. Furthermore, heart vessel damage is a characteristic feature of hyperinflammatory shock syndromes in children termed "multisystem inflammatory syndrome in children" (MIS-C), sharing similarities to "Kawasaki disease" though possesses some intrinsic specificities [31]. The pro-inflammatory cytokines are known to affect the anticoagulant pathways associated with endothelial cells which can cause thromboembolic complications, hence providing another probable pathogenic mechanism for tissue damage driven by cytokines. The cytokines though play a central role in innate immunity and are crucial for viral clearance and subsequent resolution of infections, their exaggerated release of "cytokine storm" in blood circulation is responsible for worsening the disease in almost all cases including SARS-CoV-2 infection [30, 31].

Interferons; the antiviral powerhouses and SARS-CoV-2

Interferons (IFNs) classically belong to the family of cytokines included against viral insult which are grouped into three main types namely I, II, and III. Exposure to IFNs by almost any cell of the host triggers a complex transcriptional program that induces over 300 IFN-stimulated genes (ISGs). This in turns creates an antiviral state in the cell, making the cell resistant to viral multiplication, thus rendering it refractory to the virus. It is widely established that SARS-CoV-2 is a poor inducer of Type I IFN, generally causing benign infection. An integrated immune analysis was conducted on a cohort of 50 patients with varying COVID-19 severity. Interestingly, highly impaired type I IFN response was observed among those patients, characterized by no to low IFN-β and IFN-α production. This state was found associated with exacerbated inflammatory response and persistent viremia. Further, neutralizing antibodies for IFN-I were detected in critical cases of COVID-19, accounting for approximately 20% mortality rate [32]. Low concentrations and delayed kinetics of cytosolic RNA sensors were documented by numerous studies affecting IFN-I and III in cell lines when infected with SARS-CoV-2 [33]. Many of the viral proteins are known to target different proteins in the IFN-I induction pathway: Nsp1, 5, 6, 13, ORF3a, 3b, and ORF6, among many others. NSP1 is presumed to inhibit the association of IRF3 and the promotor IFNB and subsequently inhibit IFN-I [34] by preventing the access of mRNA to ribosomes. Konno and coworkers reported the antagonistic potential of ORF3b against ISGF3 translocation to the nucleus [35]. Nsp14 was found to inhibit translation via impairment of IFN-I-dependent stimulation of ISGs. Shemesh and colleagues reported that ORF7b variants induce reduced levels of endogenous IFN-β [34]. Since IFNs possess a broad spectrum of antiviral activities and are found to be down-regulated by SARS-CoV-2, administration of recombinant IFN-α and IFN-β appears to be a promising clinical strategy for the treatment of COVID-19. Concerning this, IFN-β1a infused in inhaled nebulizers has been assessed for safety and efficacy in COVID-19 patients [36]. Future investigation aimed at the exploration of more precise insight, unveiling the exact

role played by IFN-I and III in SARS-CoV-2 infection will open up new avenues for effective COVID-19 management.

Adaptive immune response

T cell-mediated immune response

Specific cellular immunity during COVID-19 is mediated by $CD4^+$ and $CD8^+$ T cells. SARS-CoV-2 virus or viral peptides are incapable of direct activating T cells. However, it is also well established that dendritic cells, monocytes, and macrophages express ACE2, allowing SARS-CoV-2 to enter these immune cells and activate T cells, particularly $CD8^+$ T cells. It is pertinent to mention that in most cases, COVID-19 disease does not induce a pronounced inflammatory response in dendritic cells and macrophages and the levels of cytokines are nearly undetectable [37]. This may prevent their relocation to local lymphoid tissue and development to cells with the expression of co-stimulation molecules that are particularly effective at presenting antigens to recirculating T cells. This suggested that it may be challenging to produce a significant T-cell response to SARS-CoV-2, which may impede the development of immunity. The occurrence of lymphopenia or lymphocytopenia, characterized by a reduced number of T cells, is a key feature of severe SARS-CoV-2 infection. However, T cell counts in patients with moderate symptoms are frequently normal or slightly elevated. The severity of lymphopenia appears to be associated with the morbidity and mortality of COVID-19 [38]. Despite being a phenomenon found in previous viral infections, loss of peripheral T cells in moderate to severe COVID-19 patients remains mysterious. Several factors seemingly contribute to the progression of lymphopenia. One of these reported phenomena is an enhanced cell-autonomous death by apoptosis. Particularly, in most of the severe cases of COVID-19, a high level of caspases was observed. In addition, enhanced apoptosis and phosphatidylserine exposure was seen in T cells isolated from individuals affected by severe SARS-CoV-2 infection. This was linked with elevated serum levels of soluble Fas ligand with increased Fas also known as CD95 expression on T cells, specifically on $CD4^+$ T cells [39]. Consistently, over-expression of cytokines, particularly, IL-6, IL-10, and TNF-α has also been suggested to be associated with lymphopenia. T cell recirculation in the blood may be suppressed by cytokines, which promotes T cell retention in lymphoid organs and endothelial adhesion. Conversely, Xiang *et al*. found significant cell death of lymphocytes in the spleens and hilar lymph nodes of individuals who died from SARS-CoV-2 infection, which suggested roles for IL-6 and Fas-FasL interactions [40].

B cells mediated immune response

Humoral immunity is essential for the immunological clearance of pathogens and is a key component of robust memory response to prevent reinfection. The virus-specific IgM, IgG, IgA, and neutralizing IgG antibodies (nAbs), produced by B cells were profoundly observed in most COVID-19 patients [41]. Antibodies released by B cells play an essential role in the destruction of infected cells by binding to viral antigens which direct the NK cells to destroy the infected cells via antibody-dependent cell cytotoxicity. Antibodies also play a critical role in the immunological clearance of cytopathic virus, however, a mounting body of evidence suggested that some antibodies might cause aberrant B cell activation and relapse of the infection. As the secretory IgA antibody protects the respiratory tract against viral infection, it is suggested to be the most crucial immunoglobulin in neutralizing SARS-CoV-2. IgA was detected in most of the COVID-19 patient's saliva and lingered for almost three months after the onset of symptoms [42]. In the infected individuals, IgA released ahead of other immunoglobulins, lasts longer than IgM, and promotes the development of cytokines, particularly, monocyte chemoattractant proteins and IL-6. Most people infected with SARS-CoV-2 developed immunity against the virus and seroconverted within 5-15 days post-exposure. In general, somatic hypermutation is not observed in neutralizing antibodies against SARS-CoV-2. This observation suggested that naive B cells, rather than pre-existing cross-reactive memory B cells, are responsible for the development of neutralizing antibody responses to SARS-CoV-2. Therefore, it appears that neutralizing epitopes on the receptor binding domain of SARS-CoV-2 spike protein are highly immunogenic and easily identified by antibodies, especially those corresponding to the ACE2 receptor binding footprint. It is pertinent to mention that in most of the recovered cases, neutralizing antibody titers were low, implying whether the neutralizing antibody potency or the serum concentration is offensive and inappropriate. Notably, a mounting body of evidence suggested a correlation between T cell immunity and humoral response in COVID-19-recovered individuals [43]. A delay in the production of neutralizing antibodies in severe cases of SARS-CoV-2 infection than in mild cases has also been observed. These findings are consistent with the notion that $CD4^+$ T cells are necessary for maintaining T cell-dependent humoral response characteristics such as germinal center development and B cell differentiation leading to isotype switching and immunoglobulin maturation. Depletion of $CD4^+$ T cells in the lymph nodes is consistently linked to poor germinal center production in individuals with severe SARS-CoV-2 infection [43]. This delay in developing antibodies may contribute to viral spread and the prolonged latency of SARS-CoV-2 in infected individuals.

Immunotherapies against SARS-CoV-2

Convalescent plasma therapy

Convalescent plasma therapy (CPT) has been used as a treatment for COVID-19. This therapy involves collecting plasma from individuals who have recovered from COVID-19 and transfusing it into patients who are currently infected with the virus. The idea is that these plasmas contain neutralizing antibodies against a particular virus, which can help a patient's immune system fight off infection [44]. Early transfusion of convalescent plasma (CP) is more effective in improving the survival rate of critical COVID-19 patients in the early stages of the disease. This is because the viral load is generally higher in the first week of the

disease, and the early administration of CP can help neutralize the virus and prevent its further spread in the body. However, it should be noted that CP may not be useful for mild or end-stage patients. Mild patients can usually recover on their own, and end-stage patients may have disease severity that cannot be significantly improved by CP. Therefore, CP is usually recommended for patients in the moderate stage of the disease who are at risk of progressing to severe disease. The titer or concentration of SARS-CoV-2 neutralizing antibodies in CP can also affect the treatment efficacy. CP from donors who are at least three weeks after symptom onset and have a high titer of neutralizing antibodies is more efficient in treating COVID-19 patients [44].

Monoclonal antibodies

Monoclonal antibodies (mAbs) are laboratory-made proteins that mimic the immune system's ability to fight off harmful pathogens. Several monoclonal antibodies against SARS-CoV-2 are currently being developed and tested for their efficacy in treating COVID-19. Combination of Casirivimab and Imdevimab monoclonal antibodies also known as REGN-COV2, received emergency use authorization from the US Food and Drug Administration (FDA) in November 2020 [45]. Similarly, Bamlanivimab and Sotrovimab received emergency use authorization from the FDA in November 2020 and May 2021, respectively [46]. All these monoclonal antibodies are authorized for the treatment of mild to moderate COVID-19 in adult and pediatric patients who are at high risk of progressing to severe disease or hospitalization. It is important to note that the effectiveness of these treatments may vary depending on the patient's stage of illness.

Immunotherapies targeting host immune mediators

Corticosteroids, such as dexamethasone and methylprednisolone are used in COVID-19 patients to reduce lung inflammation and cytokine storm. They target host immune response and inflammatory cascades, which are important pathophysiology in SARS-CoV-2 infection. The guidelines recommend using steroids in severe cases and for those on mechanical ventilation. Similarly, dexamethasone and methylprednisolone are also commonly used due to their high lung bioavailability [47]. Dexamethasone suppresses proinflammatory cytokines but has some side effects such as fluid retention, hormonal imbalance, and disturbed sleep pattern, while methylprednisolone has a quick onset of action but can cause long-term side effects like hypokalemia and dysglycemia. Similarly, given the fact that inhibitors of tyrosine kinases can obstruct cytokine signaling and several immunological effector pathways, tyrosine kinases are considered an attractive therapeutic target to reduce COVID-19. This is validated by some experiment findings, where patients receiving oral Baricitinib had a faster recovery time from COVID-19 compared to those receiving a placebo. The effect was even more significant in patients who required high-flow oxygen or noninvasive ventilation. The median time to recovery was 7 days for those receiving Baricitinib and 8 days for those receiving a placebo [48]. Furthermore, targeting specific cytokines in a cytokine storm using monoclonal antibodies, recombinant proteins, or other methods to block their pro-inflammatory effects is a promising approach for treating SARS-CoV-2 infection. Tocilizumab, an inhibitor of the IL-6 receptor, has been evaluated for its potential in treating severe cases of COVID-19 due to its ability to target the overactive immune response of infected individuals. Clinical trials have been conducted to assess the effectiveness of this treatment approach in mitigating symptoms and improving patient outcomes. Three retrospective clinical studies have shown that Tocilizumab can reduce mortality rates in COVID-19 patients, particularly those with high levels of C-reactive protein (CRP) and systemic inflammation [49]. Similarly, it has been observed that high-dose Anakinra, an inhibitor of IL-1, administered intravenously can improve respiratory function in COVID-19 patients and potentially allow for the removal of mechanical ventilation. The results of multiple cohort studies also support this conclusion [50].

Conclusion

SARS-CoV-2 infection has had a profound impact on global health and society. The progression of COVID-19 is a result of multiple pathophysiological mechanisms, including the immune response to SARS-CoV-2 infection, which can lead to hyperinflammation and multiorgan dysfunction. Therefore, understanding the immune response to the virus is critical to improving the treatment and management of COVID-19. The diverse nature of COVID-19 pathophysiology calls for a multi-level approach with multiple treatment regimens, from antivirals in early stages to immunomodulating therapy in advanced stages. The increasing use of immunomodulatory treatments, such as monoclonal antibodies, may offer new therapeutic options for mitigating severe disease and reducing hospitalization. Additionally, the ongoing rollout of COVID-19 vaccines is expected to greatly impact the future of COVID-19 immunopathology, with data already demonstrating their efficacy in reducing the severity of disease and hospitalization rates. Furthermore, a single-pathway approach is insufficient, a multi-faceted approach is necessary to tackle the pandemic. Continued research in this field will help us to better understand the underlying mechanisms of SARS-CoV-2 infection and improve outcomes for patients.

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