Review Paper
Immune System Vs. SARS-CoV-2

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ABSTRACT

In 2019, the SARS-CoV-2 virus caused one of the biggest virus pandemics called Coronavirus disease-19 (COVID-19). This virus has been responsible for the death of millions of people around the world. The biological function of SARS-CoV-2 and its pathophysiology mechanisms, as well as the host immunity against this virus, has attracted the attention of the scientific community all over the world. The current study reviewed innate and acquired immune responses following COVID-19 infection. These immune responses are probably involved in the severity of the disease and death. Also, the cause and consequence of potential clinical strategies to treat or prevent SARS-CoV-2 infection have been proposed.

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1. Introduction

The rapid global spread of the SARS-CoV-2 coronavirus and, as a result, the 2019 coronavirus disease (COVID-19) led the world health organization (WHO) to declare this disease a pandemic on March 11, 2020. Traces of the origin of the disease were found in the city of Yuhan, Heji Province, China, where a group of people with viral pneumonia was first identified, many of whom were in contact with Yuhan seafood markets. On December 31 in 2019, China reported the outbreak of this disease to the WHO and after that, it quickly identified the pathogen, which belongs to the family of beta coronaviruses and has a high sequence homology with the bat coronavirus that enters into the host cell through the angiotensin convertase 2 enzyme (ACE2). Despite the possible animal origin of the virus, anthroponoses have been confirmed with clinical manifestations varying from asymptomatic to symptomatic including mild fever, cough, shortness of breath, cytokine release syndrome (CRS), acute respiratory distress syndrome (ARDS), multi-organ failure and death. SARS-CoV-2 has genetic and functional similarities with other two viruses, severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS), which were epidemic agents of animal origin and topical outbreaks in 2003 and 2012, respectively [1]. Even though SARS-CoV-2 has a higher amount of mild or asymptomatic people than SARS-CoV-1 and MERS [2], its significant outbreak has put high pressure and urgent consequences on the medical and public health systems of the whole world.

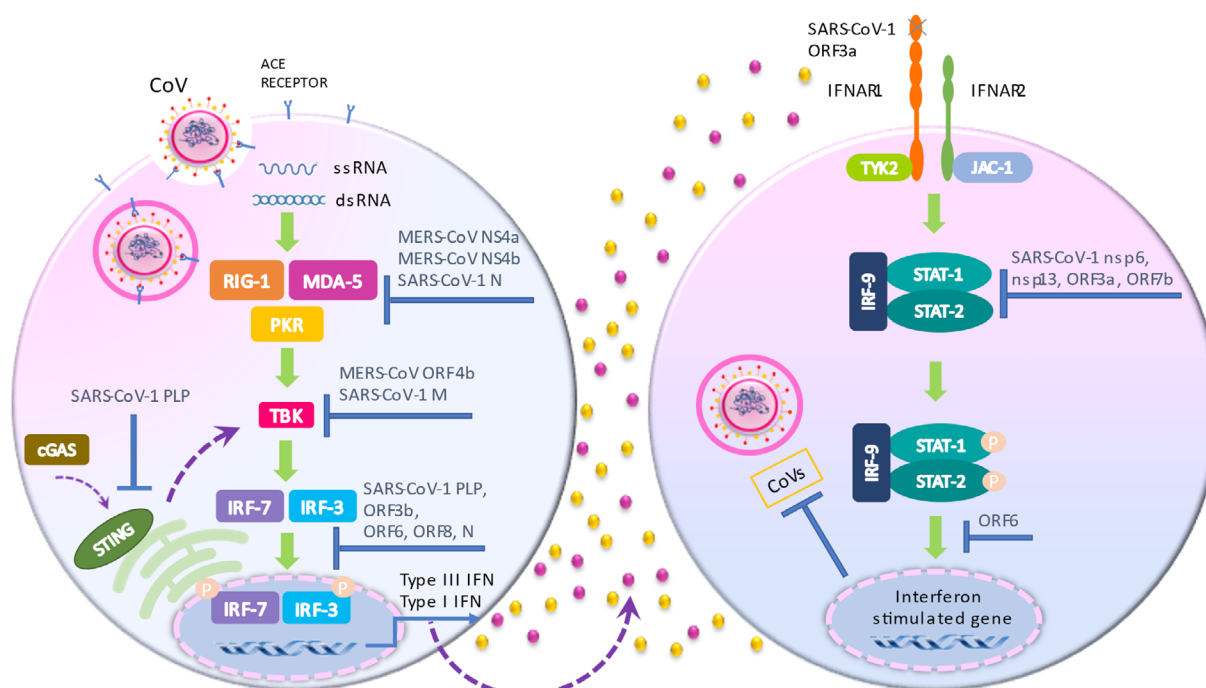### SARS-CoV-2 and innate immune responses

Recognition of pathogens via innate immunity is the first step of antiviral defense and a necessary phase for antiviral immunity. Currently, our findings of innate immune responses specific to SARS-CoV-2 are largely limited. However, considering the same sequence homology between the coronaviruses, SARS-CoV-2 virus-host interactions, and innate immune signaling mechanisms appear to be similar to other members of the coronavirus family. In the case of RNA viruses such as SARS-CoV-2, innate immunity is activated by the occupation of pattern recognition receptors (PRRs) such as RIG-I-like receptors (RLRs) within the cytosol and endosomal or extracellular Toll-like receptors (TLRs) with single-stranded RNAs or two-stranded virus. After activation of PRRs, downstream signaling pathways trigger the release of cytokines. Among them, I- and II-type interferons (IFNs) are of great importance for antiviral defense. However, other inflammatory cytokines including tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), IL-6, and IL-8 are also secreted. All these cytokines together induce antiviral programs in target cells and enhance adaptive immune responses [3]. If these responses are induced quickly and in the right place, IFN-I can effectively limit coronavirus infection. Recent evidence has shown that SARS-CoV-2 is sensitive to treatment with IFN-I/IIII in vitro, possibly more sensitive than SARS-CoV-1 [4, 5]. Studies have shown that the lymphocyte antigen 6 locus complex E (LY6E) interferes with the membrane binding of the spike (S) protein of SARS-CoV-2 [6]. Proteins of the IFN-stimulated membrane crossing (IFIM) family probably prevent the entry of SARS-CoV-2 like SARS-CoV-1.

Coronavirus escapes from innate recognition

As cytokines constitute the primary barrier to viral infection, coronaviruses employ a variety of strategies to block the signaling of IFN-1 generation. Several investigations have demonstrated that SARS-CoV-1 suppresses in vitro and in vivo IFN secretion [7, 8]. Probably, SARS-CoV-2 has similar effects, because human bronchial cell culture and a mouse model of SARS-CoV-2 showed weak IFNI/III response. Also, patients with severe COVID-19 showed impaired effects of IFN-I compared to the mild to moderate group [9]. There are several mechanisms for coronaviruses to escape from innate immunity, in which viral factor intervenes at the stage of the path of recognition, through signaling, cytokine secretion, or IFN message transmission (Figure 1).

Viruses containing single-stranded RNA, such as coronaviruses, produce double-stranded RNA intermediates during replication, which are recognized by the endosomal TLR3 receptor and PKR, MAD5, and RIG-1 receptors in the cytosol. The single-stranded RNA of the virus is also detected through TLR7, TLR8, and with high power through PKR, RIG-I. Coronaviruses prevent the activation of pattern recognition receptors by evading recognition and antagonizing the activity of PRRs [10, 11]. To escape from PRRs, the dsRNA of the SARS-CoV-1 virus is first coated with membrane components [12]. In addition, the viral RNA is capped at the 5' end by 10,13,14,16 methylated non-structural proteins (NSP) with guanosine. As a result, the host mRNA strengthens the translation process, prevents its degradation, and avoids recognition through PRRs [10, 11]. Finally, coronaviruses produce an endonuclease called NSP15, which cleaves the poly uridine at the 5' end of the viral RNA and prevents recognition of the virus by MDA5. Several techniques are also employed by coronaviruses to inhibit the activation of PRRs. The N protein SARS-CoV-1 inhibits RIG-1-mediated activation of TRIM25. In addi-

Figure 1. Coronaviruses Interventions in host innate immune response. Overview of innate immune recognition (left) and interferon signaling (right), along with known mechanisms by which SARS-CoV-1 and MERS-CoV interfere with message signaling.

tion, the NS4a protein of the MERS-CoV virus inhibits the activity of PKR by binding to the double-stranded RNA of the virus and inhibits PACT, which activates RLRs. Moreover, the NS4b protein of MERS-CoV inhibits RNaseL, another RLR activator [13].

The function of other PRRs remains unknown. For instance, papain-like protease (PLP) is an antagonist of STING. As a result, it is possible that internal DNA can be an important driver [14]. However, which SARS-CoV-2 homolog overlaps with this function remains unclear.

After activation, RLR and TLR receptors trigger signaling cascades that result in the phosphorylation of transcription factors such as NF-κB and the interferon regulatory factor (IRF) family and the production of inflammatory cytokines and interferon. Proteomic investigations have revealed links between SARS-CoV-2 proteins and the PRR signaling cascades, even though in vitro studies have not determined the precise faction of SARS-CoV-2 proteins. SARS-CoV-2 ORF9b protein interacts indirectly with the MAVS signaling adaptor via interaction with Tom70 [15]. In addition, the NSP13 protein of the SARS-CoV-2 virus mediates TBK1 signaling and the NSP15 protein interacts with RNF41, which activates TBK1 and IRF3. Similarly, the SARS-CoV-1 virus M protein and MERS virus ORF4b protein inhibit

the TBK1 signaling complex [15]. Other proteins including PLP, N, ORF3b, and ORF6b of the SARS-CoV-1 virus prevent the phosphorylation of IRF3 and its transfer to the nucleus [16]. The proteins of coronaviruses suppress NF-κB as well. PLP of SARS-CoV-1 and ORF4b and ORF5 proteins of the MERS-CoV virus is among these proteins [17]. Lastly, the NSP4 protein of SARS-CoV-1 and MERS-CoV viruses interferes with host transcription and translation, hence restricting non-specific antiviral responses [18].

To prevent downstream signaling of IFN, coronavirus proteins disrupt multiple steps in the message transmission route that connects interferon receptor subunits (IFNR1, IFNR2) and STAT transcription activator proteins. In the case of SARS-CoV-1, these mechanisms consist of the destruction of IFNAK1 by ORF3a, the lowering of STAT1 phosphorylation via NSP1, and the inhibition of STAT1 nuclear translocation via ORF6 [8, 17]. Nevertheless, the ORF6 protein of SARS-CoV-2 shares just 69% of its sequence homology with SARS-CoV-1. Therefore, its performance may not be entirely safeguarded. The lack of restriction of STAT1 phosphorylation in SARS-CoV-2 infection compared to SARS-CoV-1 also confirms the above suggestion [19].

Misbalancing between inflammatory and antiviral responses

As mentioned, pathogenic coronaviruses use several strategies to evade innate immune recognition, particularly the IFN pathway, to have a special function in the pathogenesis of COVID-19 by disrupting the IFN responses. In line with these results, in infected animal models with SARS-CoV-1 and MERS-CoV, the relationship between the failure to generate initial IFN responses and the severity of the disease has been determined [3]. According to these models, perhaps more important than anything else is the issue of time, because the presence of IFN at the beginning of the disease can be protective but harmful in delayed responses. Probably, the increase in ACE2 expression by interferon in epithelial cells of the airways plays a role in this relationship. Additionally, while pathogenic coronaviruses block IFN signaling, they can increase other inflammatory pathways involved in disease pathogenesis [20]. For example, ORF3a, ORF8b, and E protein of the SARS-CoV-1 virus increase the activity of the inflammasome and the secretion of IL-1β and IL-18 cytokines, which probably play a role in pathological inflammation [21, 22]. Altogether, these inflammatory processes probably play a role in the formation of the cytokine storm seen in COVID-19 patients, leaving evidence for immunosuppressive targets. Hence, a complete understanding of the balance between innate immune and antiviral programs is necessary to identify biomarkers of effective therapeutic strategies for COVID-19 disease.

Myeloid cells

Myeloid cells with specialized characteristics, such as common dendritic cells (cDC), monocyte dendritic cells (mDC), plasmacytoid dendritic cells (pDC), and macrophages, coordinate and regulate mucosal immune responses to pathogenic agents [23]. According to the abundance of evidence, the COVID-19 syndrome is characterized by dysregulated myeloid responses. These features include cytokine storm syndrome (CRS), acute respiratory distress syndrome (ARDS), and lymphopenia [24].

Characterization of myeloid cells in COVID-19

A flow cytometry study has reported an increase in GM-CSF producing activated T cells and CD14+HLA-DR^{lo} inflammatory monocytes (IMs) in the population of peripheral blood mononuclear cells in symptomatic individuals with COVID-19 [25]. This finding is following single-cell transcriptome (sc-RNA-seq) data. In this study, CD14+IL-1β+ myocytic expansion acquired immune responses caused by mitogen-interferon-activated protein kinase (MAPK), and IL-1β mediated inflammasome characteristics were seen in the peripheral blood of patients with COVID-19. Although the systemic level of IL-1β was remarkably low, it is interesting that this manifestation of immune responses is associated with the progress of the clinical process of patients. sc-RNA-seq analyses of lung tissue from critically ill COVID-19 patients have declared an increase in IMs and Ficolin-1+ monocyte-derived macrophages to compensate for tissue-based reparative alveolar macrophages (AM) [26]. Also, discussed in this study are the effects of IFN signaling and the activation of monocyte, which likely contribute to the quick loss of alveolar structure and the progression of ARDS. Although most of the clinical attention has been on lung injury and mononuclear phagocyte (MNP) dysfunction, it is clear that COVID-19 poses systemic challenges in other organs, including the kidneys and gut. It will be crucial to comprehend the role of non-pulmonary myeloid cells in the tissue-specific pathology associated with COVID-19.

Prior Knowledge of SARS-CoV-1, MERS-CoV, and Murine Coronaviruses

While data on COVID-19 cases continue to grow, information on myeloid dysfunction in SARS-CoV-1 and MERS-CoV can be used to identify the pathogenesis of COVID-19 (Figure 2). A murine model infected with SARS-CoV-1 has exhibited an abnormal AM phenotype, leading to restricted DC traffic and T cell activation [27]. In addition, YM1+ FIZZ1+ alternative macrophages can exacerbate airway hypersensitivity and SARS-associated fibrosis [29]. In addition, as stated previously, murine SARS-CoV-1 studies have implicated delayed IFN-I signaling and the presence of inflammatory monocyte-macrophages as the cause of elevated levels of cytokines and chemokines, vascular leakage, and defective antigen-specific T cell responses in the lung of this disease. They know it is fatal [3]. Alveolar interstitial pneumonia with infiltration of lymphocytes and monocytes and accumulation of macrophages in the alveolar lumen has been observed in mice expressing human hACE2, confirming human findings [29]. Finally, nonhuman primate studies and patient data on SARS-CoV-1 have shown that spike virus-specific IgG attenuates acute lung injury by driving alveolar macrophages toward an inflammatory phenotype and increasing the recruitment of inflammatory monocytes via CCL2 and IL-8 Intensifies [30]. However, the investigation of which antibody response is involved in disease pathology remains to be determined.
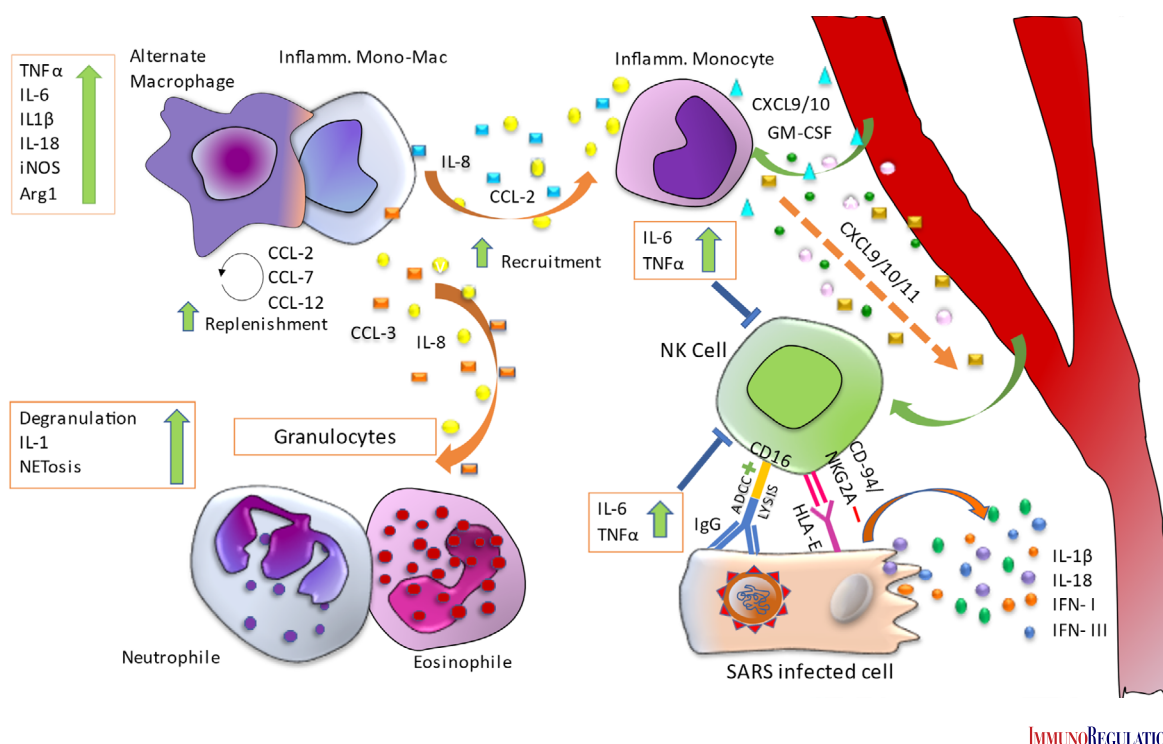
Figure 2. Results of SARS-Cov-2 infection in myeloid cell activation and altered NK cell function

SARS-CoV-2 infection and dysfunction of NK cells

The ex-vivo study conducted on peripheral blood NK cells of patients with COVID-19 shows that the intracellular expression of CD-107a, KSP37, Granzyme B, and Granulysin is reduced, indicating a disruption in cytotoxic activity and production of chemokines, IFN-ɤ, and TNF-α in these cells [31]. Multiple mechanisms may contribute to NK cells dysregulation. During influenza infection, infected NK cells undergo apoptosis. As pulmonary NK cells do not express the ACE-2, direct infection by SARS-CoV-2 is unlikely. The majority of CD16^{+}, KIR^{+} CD56^{dim} NK cells in the lung are capable of inducing cytotoxicity in response to HLA-I or FC receptor signaling, even though this proportion is lesser than that of NKs in the peripheral blood [32].

For the cytolytic activity of NK cells, the expression of KIR and CD16 receptors is necessary. These receptors are expressed during the development of NK cells. The expression frequency of CD16 or KIR on peripheral blood NK cells decreases in SARS-CoV-1 and SARS-CoV-2 infection, respectively [33].

In general, the results indicate that in patients with COVID-19, there is a disruption in the maturation of NK cells or the migration of NK cells from the peripheral blood to other peripheral tissues.

In the case of SARS-CoV-2 immune checkpoint NK-G2A on T CD8^{+} and NK cells is expressed more than physiological condition. Interaction between NKG2A and non-classical HLA-E molecules impedes cell lysis [34].

Also, the expression level of Tim-3 and LAG-3 coding genes increase the amount of NK cells in COVID-19 individuals. Therefore, increased expression of the immune checkpoint on NK cells can play a key role in virus escape. In addition, in infected patients the serum level of IL-6 increases, which is significantly related to the decrease in the number of NK cells [9, 35].

In COVID-19 patients, the TNF-α serum level is increased. Peripheral blood sc-RNA-seq findings show that TNF-α secreted by monocytes can bind to its receptors on the surface of NK cells. TNF-α is also involved in the differentiation of NK cells through the reduction of NKP46, although no effect of TNF-α or IL-6 on NK-mediated ADCC has not been reported to date. Collectively, these findings suggest that intermittent NK engagement with monocytes may lead to impaired recognition and killing of SARS-CoV-2 virus-infected cells by NK cells, and Abs against IL-6, and TNF-α signaling. It can be beneficial for COVID-19 patients by increasing the function of NK cells [36].

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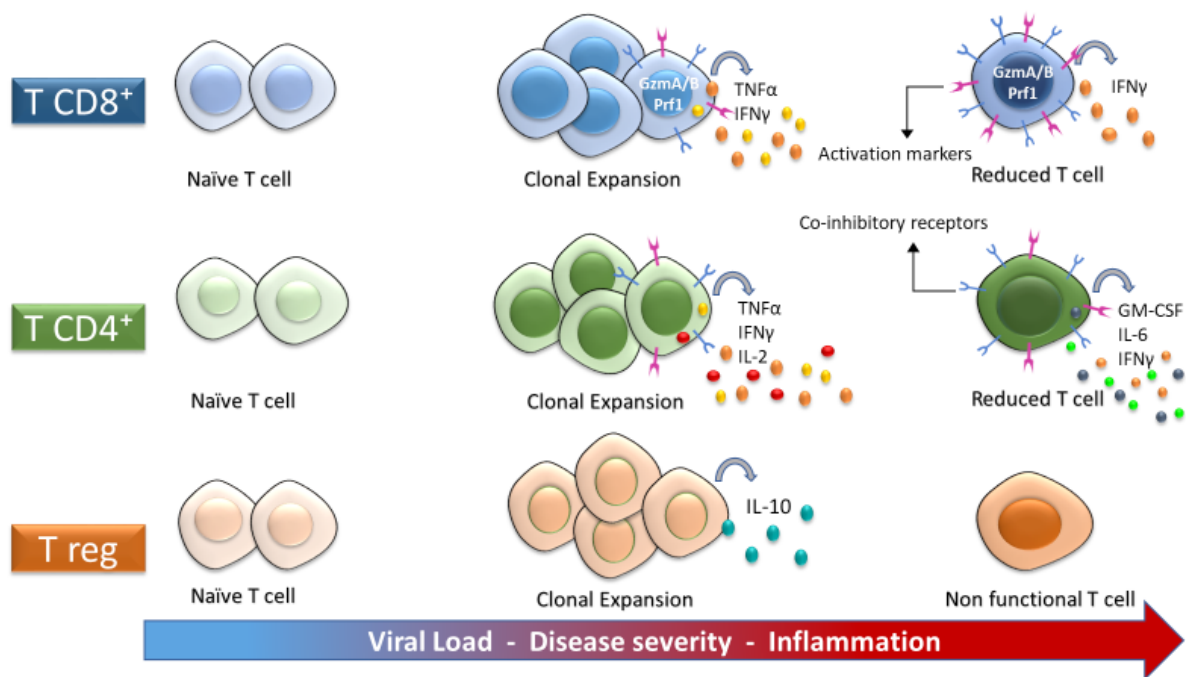
Figure 3. T Cell response to SARS-CoV-2: changes in peripheral blood T cell frequencies and phenotype.

Complement activation

Complement proteins are part of innate immunity, and new research has linked complement activation to the pathophysiology of ARDS. C3 is one of the most important complement components causing pathogenesis in the case of SARS-CoV infection. In addition, research has shown that depleting C3 in mice infected with SARS-CoV reduces lung damage. C3-deficient mice exhibit lower amounts of IL-6 and other chemokines and cytokines, as well as lower neutrophil and monocyte influx [37]. Several investigations have demonstrated the role of complement activation in COVID-19. C5b-9 and C5a complement components were found to be significantly higher in the plasma of severe COVID-19 patients [38]. According to the findings of Gao et al., binding of the N protein of the SARS-CoV family to mannan-binding lectin-associated serine protease 2 (MASP-2) can induce aberrant activation of complement and pulmonary damage. Therefore, inhibiting this interaction may reduce inflammation and lung pathogenesis [39]. Complement stimulation can also cause coagulation, thrombosis, and microvascular damage, as seen in a large number of CO-VID-19 patients [40-42]. Furthermore, the accumulation of C5b-9, C4d, and MASP-2 products can cause vascular complications in COVID-19 patients [42]. It has also been reported that the increase in C5b-9 deposition in the kidney tubule of COVID-19 patients can cause damage and kidney failure [43]. Treatment with anti-C3 such as

AMY-101 and inhibitors of the complement activation pathway such as the lectin pathway might assist COVID-19 patients to avoid lung injury [37].

Innate lymphoid cells (ILC) in infection with SARS-Cov-2

COVID-19 patients compared to healthy individuals have exhibited significantly lower levels of innate lymphoid cells in their blood. The remaining circulating ILCs exhibited lower ILC2 frequencies in severe COVID-19 patients, with a concurrent drop in ILC precursors (ILCp) in all patients as compared to controls. ILC2 and ILCp exhibited an activated phenotype with enhanced CD69 expression, but CXCR3 and CCR4 expression levels were dramatically changed in ILC2 and ILCp, and ILC1, respectively. The activated ILC profile of COVID-19 patients was linked to soluble inflammatory markers, while ILC subset frequencies were associated with laboratory parameters that reflect disease severity [44].

T cell response

T cells are one of the most important components in immunity against viral infections. Activated CD4+T cells release cytokines, which stimulate the activation of other immune cells, particularly B cells, to produce antibodies against pathogens and develop immunity. TCD4+ T cells can also assist CD8+ T cells in their ability to directly kill virus-infected target cells. Immunopathology can be

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brought on by T cell malfunction. Understanding the role of T cell's response in the initial suppression of the virus and tissue damage during COVID-19 infection and the act of memory T cells in the progression of immunity following viral infection will help us better understand how T cells react to SARS-CoV-2 infection.

Total reduction of TCD4^{+} and TCD8^{+} Cells in peripheral blood

Studies indicate that similar to infection with SARS-CoV-1, in moderate and severe patients with COVID-19, lymphopenia occurs with a significant decrease in TCD4^{+} and TCD8^{+} cells [45]. It seems that the degree of lymphopenia is related to the severity of the disease and the death rate caused by it, especially in patients hospitalized in the ICU. In mild patients with COVID-19, the number of T cells is normal or slightly enhanced [46]. In moderate to severe patients previously exposed to COVID-19, the number of T cells decreases. Although this phenomenon occurs in infection with other virus infections, the reason is not clear, and unlike MERS-COV infection, direct infection of T cells has not been reported (Figure 3).

The mechanisms that may play a role in the reduction of T cells can be mentioned as the effect of the inflammatory environment caused by inflammatory cytokines. In fact, in these patients, lymphopenia seems to be related to the serum levels of IL-6, IL-10, and TNF-α, so that in recovered patients, the return of T cells is related to the overall decrease in the level of inflammatory cytokines. Some factors such as IFN-I and TNF-α may prevent T cells from returning to the bloodstream through retention in lymphoid organs and attachment to the endothelium [47].

Analyzing autopsy samples of spleen and hilar lymph nodules of 6 patients with COVID-19, Chen et al. showed that lymphocytes undergo widespread cell death, which can be caused by penile IL-6 as well as Fas-FasL interactions.

In support of this hypothesis, it has been reported in a study that the drug tocilizumab, as an IL-6R antagonist, increases the number of circulating lymphocytes. T cells can be reduced in the peripheral circulation by directing them to the sites of infection. sc-RNA-seq analysis of BAL samples of COVID-19 patients indicates increased penetration of TCD8 cells along with clonal expansion [48].

Also, the study of the lung of the patient who died as a result of ARDS following COVID-19 showed that there is extensive lymphocyte infiltration in the lung of this patient. While in another study studying the lungs of 4 patients who died due to COVID-19, only neutrophilic infiltration was reported. Further research appears to be required to determine the source and consequence of the lymphopenia found in COVID-19 patients.

Induction of antiviral responses of T cells

The available data about specific T cell immunity against SARS-CoV-1 can be used as a guide to better understand SARS-CoV-2 infection. Although in SARS-CoV-1 infection, TCD4^{+} responses are limited to protein S, the immunogenic epitopes of T cells are against ORF-3, M, N, and proteins S of the SARS-CoV-1 virus.

In SARS-CoV-1 survivors, the size and abundance of virus-specific TCD8^{+} memory cells are more than TCD4^{+} memory cells, and virus-specific T cells are stable for at least 6-11 years, which indicates that T cells can play a role in long-term immunity [49].

Limited data from patients with SARS suggest that virus-specific TCD4^{+} cell numbers may be related to greater disease severity, and increased Th-2 cells are associated with mortality from this virus. However, investigating the quality of TCD4^{+} responses is needed to understand their relationship with the severity of the disease. So far, few studies have been conducted regarding the specific immunity of T cells in SARS-CoV-2 infection. The results of IFN-ɤ ELISPOT investigation in 12 mild COVID-19 patients indicate the presence of specific T responses for viral S, M, and N proteins. In another study, it has been shown that in 1/3 of patients after recovery, only N protein-specific T cells can be identified [50].

The results of the study of patients with moderate to severe ARDS following COVID-19, two weeks after admission to ICU, using flow cytometry technique, show that the average frequency of CD4 T cells and CD8 T cells in all patients is 1.4% and 1.3%, respectively, and the very limited immunophenotype of these cells based on the expression of TCD45RA and CCR7 indicates that they are mostly TCD4^{+} central memory or TCD8+ effector memory and effector memory RA (TEMRA) [45]. This study is crucial for the utilization of the 1095 epitope of SARS-CoV-2 as a specific stimulating antigen and shows that both TCD4^{+} and TCD8^{+} cells have a preferential specificity for S protein and 10-30 days after the onset of symptoms [51].

Further investigations of protein S-specific T cells by single-ELISA show strong induction of IFN-ɤ, TNF-α, and IL-12 together with lesser levels of IL-5, IL-13, IL-9, IL-10, IL-22 [52].

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In another study, by examining the specific TCD4+ responses of protein S in 18 patients with mild, severe, and critical COVID-19 using an overlapping peptide pool, they showed that in 83% of cases, TCD4+ cells with the simultaneous expression of CD137CD154 as cells Anti-viral TCD4+ are present and the increased expression of CD38, HLA-DR, and Ki-67 indicates recent activity in vivo. It is noteworthy that the authors have identified a lower frequency of TCD4+ cells reactive with S in 34% of the healthy control group. These cells have a lack of activation markers and are specific for the C-terminal S protein, which is very similar in endemic human coronaviruses and can indicate that TCD4+ memory cells are cross-reactive in some populations (such as children and young patients with a history of hCoV infections) [52].

Similarly, endemic coronavirus-specific TCD4 cells have previously been shown to recognize SARS-CoV-1 agents. Further research is required to determine how former infections with endemic coronaviruses may change immune responses to SARS-CoV-2. The results of TCR-Seq studies indicate that the level of TCR-Clonality in blood circulation and BAL is higher in mild patients compared to severe COVID-19 patients [53].

T Cells› role in promoting COVID-19 inflammation

While high T-cell immunity is required for successful viral management, disruption of T-immune responses may produce immunopathology and contribute to disease severity in COVID-19 patients.

Zhou et al. have reported that the frequency of polyclonal GM-CSF+ TCD4+ cells, which can produce IFN-ɤ and IL-6 in ex vivo conditions, only in severe COVID-19 patients, increases. It is noteworthy that it has been previously reported that GM-CSF+ TCD4+ cells play a role in inflammatory autoimmune diseases such as MS or jRA as well as brain sepsis [54].

It has also been reported in two studies that the frequency of Treg cells decreases in severe COVID-19 cases. Although Treg cells have been demonstrated to progress inflammation in the ARDS mouse model, the reduction of these cells can have a key role in the lung immunopathology of people infected with COVID-19. Similarly, Tɣδ cells, as a subset of T cells that play a protective antiviral role in influenza-induced pneumonia, are also reduced in severe COVID-19 patients [55].

T cell subgroup phenotype and function in COVID-19

In most studies, there are reports of the increased presence of activated T cells that express markers such as HLADR, CD38, CD69, CD25, CD44, and Ki67 [52].

In general, regardless of the severity of the disease of COVID-19, TCD8 cells seem to be more active than TCD4 cells in this disease. This phenomenon has also been seen in SARS-CoV-1 disease. In a report of 10 COVID-19 patients, PD-1 levels enhanced from the early to symptomatic phases of the disease. PD-1 expression is normally associated with T cell fatigue, although it is crucial to highlight that it is predominantly triggered by TCR signaling and is also expressed by active effector T cells [56].

Moreover, numerous studies have reported the high expression of several stimulatory and inhibitory molecules such as OX40, CD137, CTLA4, TIGIT, and NKG2a. Also, a decline in the number of TCD8+ CD28+ cells and an increase in TCD8+ PD1+ TIM3+ cells have been reported in patients hospitalized in ICU. The expression of most of these markers on TCD8+ cells is higher than on TCD4+ cells, and in more severe patients, it is higher, which probably indicates that it is related to the viral load. It has also been shown that the cellular activity of TCD4+, and TCD8+ cells such as the production of cytokines IFN-ɤ and TNF-α subsequently. Cell stimulation is reduced with PMA and ionomycin in critical patients [45].

Zheng et al. showed that in severe COVID-19 patients, the cytotoxic and executive activity of TCD8+ cells, including CD107a degranulation and Genzyme B production, is reduced [34].

On the other hand, in another study, it has been shown that in severe patients, the amount of perforin and Genzyme B in T cells increases. In line with this study, it has been reported in a study that in severe patients with SARS-CoV-1 who have recovered compared to the group of moderate patients, the frequency of CD4T cells producing IFN-ɤ, TNF-α, and IL-2 CD8T cells producing IFN-ɤ, TNF-α, and CD-107a are significantly higher.

These findings are not necessarily contradictory. The sampling time and stage of the disease can affect the dynamics of T cell responses, morphology, and function. Liao et al., by RNA-Seq analysis of BAL samples, showed that in severe COVID-19 patients, TCD8+ cells express more cytotoxic genes including GZM A, and GZM B, while in mild cases the expression of KLRC1 and XCL1 is higher [57].

In summary, it seems that T cells are more activated in severe COVID-19 patients and show a tendency to exhaustion based on the constant expression of inhibitory markers such as PD-1 and TIM-3, decreased activity, and cytotoxicity. On the other hand, in recovered patients, an increase in the number of follicular helpers TCD4+ population, an increase in effector molecules such as GZM A, GZM B, and perforin, and a decrease in inflammatory markers can be seen.

B cells response in COVID-19 infection

Humoral immunity is necessary to clear viruses. Also, it is an important part of memory immunity to prevent re-contamination of surfaces. Evidence for a strong B-cell response includes the quick and almost universal detection of virus-specific IgG, IgA, and IgM and neutralizing IgG in the days after infection. Similar to infection with SARS-CoV-1, in most COVID-19 patients, class switching occurs between 7 to 14 days after the onset of symptoms and antibodies titers persevere for several weeks after virus clearance. Abs against SARS-CoV-2 that bind to the internal domain of protein N and the external part of S protein is usually detected. The domain binding to the S protein receptor is more immunological, and the antibodies that bind to this domain have the potential to neutralize and block the interaction of this component with ACE-2, as the host's entry receptor [58].

Anti-RBD neutralizing Abs have been identified in most patients. Although cross-reactivity of the N and S proteins of SARS-CoV-1 and the S protein of MERS-CoV have been reported in the serum of COVID-19 individuals, no cross-reactivity with the RBD of SARS-CoV-1 and MERS-CoV viruses has been found [59].

Furthermore, plasma from COVID-19 patients does not neutralize SARS-CoV-1 and MERS-CoV. RBD-specific CD19 IgG+ memory B cells were identified from day 9 to day 28 after symptom onset. The results of antibody gene sequencing show that 209 SARS-CoV-2 specific monoclonal Abs have been generated [59]. On the other hand, in the case of COVID-19 infection, two RBD-specific Abs were recognized which do not cross-react with the RBD of SARS-CoV-1 and MERS-CoV [59].

Collectively, the result indicates that neutralizing antibodies neutralizes the virus and probably these antibodies bind to antigenic determinant within the RBD.

Memory B cell subsets

The B cell's response against viral infections is not limited to the infectious stages and viral involvement, but the most important event of the presence of B cells is related to the creation of immunity against subsequent infections. This happens through the production of plasma cells and the secretion of antibodies. The production of plasma cells with a long lifespan creates a high defense readiness against the reappearance of the virus and a faster and more intense response of the immune system to infection.

According to research, the presence of CD27Hi CD38Hi antibody-secreting cells in persons with COVID-19 provides immunity in addition to follicular T cells (Thf), such that IgG-secreting memory cells create 28-day immunity in the person is infected. In this context, investigations on SARS-COV-1 and MERS viruses have been undertaken, which can provide a clear viewpoint due to viral similarities with SARS-COV-2. According to one of these studies, SARS-COV-1 specific IgG was detectable in a person's serum 12 years after infection, and this antibody specifically for the MERS virus was detectable in a person's serum up to 3 years after infection. This duration is substantially shorter for the COVID-19 virus, and under ideal conditions, specific IgG can be identified 60 days after infection [29, 59].

Another research found that independent of age, gender, primary blood types, or clinical symptoms, the majority of recovered persons with COVID-19 acquired an IgG antibody response to SARS-CoV-2 and a protective level over a period of up to 9 months [60].

Based on the result of Pablo et al. optimal protective immunity induced by COVID-19 infection may depend on the formation of memory T cells and long-lived plasma cells from the germinal center. In the face of severe illness, there is significant evidence of immune system redundancy and variety, which guarantees a level of protection against infection when one branch of immunity is impaired. The discovery of strong memory CD8+ and CD4+ T cell responses evoked during asymptomatic infections, even in the absence of detectable antibody responses, enhances our expectations for SARS-CoV-2 protective immunity. However, achieving a robust CD8+ memory T cell response through vaccination can be difficult, and this can be highly dependent on the induction of potent, high-affinity neutralizing antibodies [61].

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2. Conclusion

SARS-CoV-2 presents a public health emergency with an unparalleled challenge for the overreach of successful treatments. SARS-CoV-2 infection disrupts the immune system leading to various inflammatory responses and in severe cases death, but no specific treatment for COVID-19 is available so far. Therefore, identifying a potential therapeutic compound against COVID-19 is of particular importance. Investigating various immunological mechanisms against SARS-CoV-2 is necessary to better understand the immunopathogenesis of SARS-CoV-2 for the treatment of COVID-19. Controlling the inflammatory response is critical to target viral infection, and therefore, it is essential to further investigate the mechanisms behind hyperinflammation to create a reliable therapeutic plan to limit viral spread.

Ethical Considerations

Compliance with ethical guidelines

There is no ethical principle to be considered in doing this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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