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SARS-CoV-2 and Manipulating the Immune System

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ABSTRACT

The novel coronavirus disease 2019 (COVID-19) that is induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a global pandemic, with more than five million death. Patients can develop pneumonia, severe symptoms of acute respiratory distress syndrome (ARDS), and multiple organ failure. Similar to other viral respiratory infections, immune responses have a prominent role in SARS-CoV-2 infection. Despite the understanding of the immune response to COVID-19, there are still major gaps in understanding controversial reactions that impact infection fate and it remains unclear to what extent these responses are helpful or harmful in COVID-19. Thus, the purpose of this review is to discuss virology of the SARS-CoV-2, viral infection and immune characteristics, immune escape mechanisms and virus strategies in manipulating immune cells such as NK cells, Dendritic cells, T cells and B cells that converts it to the defective system, particularly in severe disease. Finally, we highlight the relevance of these tactics in determining infection fate.

Keywords: Novel coronavirus, COVID-19, SARS-CoV-2, Immune response, Infection fate

INTRODUCTION

The COVID-19 disease induced by severe acute respiratory syndrome coronavirus 2 is a global pandemic with more than 200 million infections and 5 million deaths of 1 November 2021, as stated by the COVID-19 statistics of the Johns Hopkins Coronavirus Resource Center. On 11 March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic [1]. SARS-CoV-2 infection can result in a range of clinical manifestations, from asymptomatic or mild infection to severe SARS-CoV-2 that requires hospitalization. Patients hospitalized often progress to severe pneumonia and ARDS and multiple organ failure [2,3,4,5,6].

Although we have limited information about the immunological features of peoples who are asymptomatic or with mild symptoms that do not need hospitalization, new researches have shown significant insights into hospitalized patients' immune responses. Similar to other viral respiratory infections, immune responses have a prominent role in SARS-CoV-2 infection [7,8,9,10].

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Growing proof confirms that immune patterns are strictly correlated with the disease progression of virus-infected cases. A decrease in peripheral T cell subsets and cytokine storm are hallmarks in patients with severe acute respiratory syndrome [11,12]. Since, there is a narrow border between effective immune response and defective immune response and also infection fate in COVID-19, this review, summarized COVID-19's immune characteristics and discuss how SARS-CoV-2 employs complex strategies to manipulate the immune system to shift effective immune response into the defective response.

VIROLOGY OF SARS-CoV-2

Coronaviruses (CoVs) are single positive-strand, enveloped RNA viruses belonging to the subfamily Coronavirinae, which cause infection in mammals and several other animals [13]. Seven CoVs are identified to cause disease in humans and can be divided into high and low pathogenic CoVs. Three highly pathogenic, novel zoonotic CoVs have emerged during the last two decades, which can cause outbreaks and lethal human disease. In addition to the recent SARS-CoV-2, the SARS coronavirus

(SARS-CoV-1) was discovered in November 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in June 2012. Both of these viruses prompted local outbreaks and were restrained before a global pandemic. Four low pathogenic CoVs, 229E, NL63, OC43, and HKU1, cause mild diseases and are endemic globally. They are called non-SARS-like CoVs. [14,15,16].

The S Protein is the best studied of the coronavirus's proteins. This protein contains the Receptor-Binding-Domain (RBD) for the ligand on the host cell membrane. It has epitopes recognized by T and B cells, which induce immune responses [17]. The S protein is a type I (SP1) trimeric glycoprotein and protrudes from the membrane of the virion, giving the virus a crown appearance. The S protein is formed by two subunits: S1, which contains the RBD, and S2 that is responsible for the virion fusion with the host cell membrane [18,19,20]. The virus uses one cell surface protease **(**TMPRSS2, located on respiratory cells) for fusion [21]. Then viral genome injects into the cells. After RNA entry, its translate to non-structural proteins [22] that suppress host protein synthesis [23,24]. Remodeling of the endoplasmic reticulum is an example of manipulating the cells to provide the safe manufacture in favor to replicate more RNA and protein [25]. Finally, the viral proteins and genome assemble into a complete virus particle which is then transported into the cell surface through the Golgi pathway [22]. Studies show that the Angiotensin-converting enzyme 2 (ACE2) host receptor is required for host cell entry of SARS-CoV-2 [26,27]. The expression of ACE2 receptors is not restricted to the lungs, most human tissues, such as the gastrointestinal tract, heart, blood vessels, and kidney expressing ACE2 receptors [28,29]. So these tissues could be prone to SARS-CoV-2 infection [30]. In addition to ACE2, other receptors have contributions to COVID infection. For instance, the viral entry of SARS-CoV-2 has been further found to be prevented by a clinically proven inhibitor of the cellular host type 2 transmembrane serine protease TMPRSS2 [1,26].

VIRAL INFECTION AND EARLY IMMUNOLOGICAL EVENTS

Following the virus entry into the nasal cavity due to inhalation of droplets from an infected person's cough, the upper respiratory tract's epithelial cells infect at an early stage *via* the ACE2 binding receptor (days 1 to 2 after the virus enters) [31]. Viral RNA localizes in mitochondria, manipulated it and hides itself to facilitate virus replication [32]. According to clinical reports, the person was considered asymptomatic during five days of virus entry. The virus load then decreases in the upper respiratory and move to the lower respiratory tract [33,34]. During virus replication, infected cells detect viral components by innate immune sensors such as TLR3, TLR7, TLR8, RIG-1, and NLRs that activate protein adapters and signal IRF, NF-kβ, AP-1 pathways. The consequence is the development of antiviral interferons IFN-β and IFN-γ as the first antiviral defense line [35,36,37]. The host cells are severely damaged because the virus triggers the cell lysis. A focal inflammation follows this event at the site of the damaged cells. This inflammation is a calling message for the recruitment of different types of immune cells. Following the chemokine CXCL10 (IP-10) elevation, the migration of monocytes/macrophages, NK, T cells, and dendritic cells increases to the lungs [20,38]. This stage will have different consequences depending on whether the immune response process follows a normal or a disturbed path [39,40]. If the immune response is a normal response, it will activate B and T lymphocytes effectively, and effective immune response against the viral infection will occur, which will eventually lead to the treatment of the disease. More than 80% of patients at this stage show mild to moderate symptoms during 11.5 days after infection [31,41]. However, if the immune response takes an abnormal pathway, severe general damage will occur to various parts of the body, especially the respiratory system, *i.e.*, the lungs, resulting in an inflammatory form of cell death in the lung tissue results in known as Pyroptosis [42] (Fig. 1).

The result of both of these pathways is widespread local inflammation and the production of inflammatory cytokines and chemokines such as IL-6, IFN-γ, MCPI, and IP-10 [2,43]. These events are an invitation for more and more inflammations and damages and organ failures. An abnormal and unregulated immune response worsens the SARS-CoV-2 infected patient status step by step to death.

IMMUNE ESCAPE MECHANISMS

The coronavirus's immune evasion begins from PRRs. During replication of ssRNA, viruses produce dsRNA

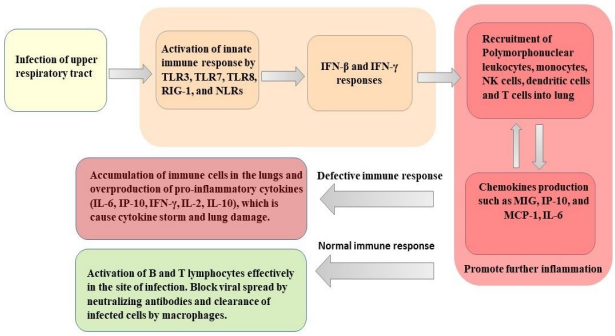

Fig. 1. Hierarchy of immunological events during infection with SARS-CoV-2. The intensity of the red color indicates the severity of the inflammation. The green color is a healthy situation.

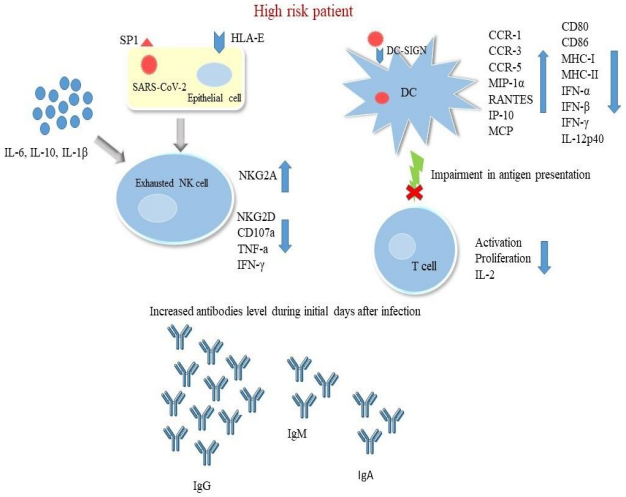

Fig. 2. Mechanisms that lead to the manipulation of immune cells and their functional failure. SARS-CoV-2 defects NK cell function by infecting epithelial cells and inducing inflammatory cytokines. On the other hand, by infecting the Dendritic cells, maturation and antigen presentation to T cells are disrupted. Antibodies, although they can prevent the spread of the virus, but their increase in the early weeks of the infection leads to disease progression.

mediators [44]. dsRNA is protected by membrane-enclosed chambers formed during viral replication of SARS-CoV-1 to escape PRRs detection [44,45]. Also, viral RNA is coated and methylated with guanosine by unstructured CoV proteins (NSPs) [44]. On the other hand, cytokines are a significant barrier to viral infection; coronaviruses have many mechanisms to suppress IFN-I induction and signaling. Following viral infection and innate immune response activation, RLR and TLR receptors activate signal cascades that lead to phosphorylation of transcription factors such as NF-kβ and the Interferon Regulatory Factor (IRF) family, eventually leading to IFN transcription and pro-inflammatory cytokines [37]. Although no experimental studies have been established on SARS-CoV-2 proteins, proteomics studies have shown interactions between viral proteins and PRR signaling cascades. Several studies have shown that SARS-CoV-1 inhibits in vitro and in vivo IFN release [44,46,47,48]. SARS-CoV-2 probably has a similar effect, with no development of IFN type I/III from infected cell lines and primary bronchial cells [49]. This pattern was observed in patients with a severe form. They had significantly impaired IFN-I production than mild and moderate disease [50].

MANIPULATING NK CELLS RESPONSE

NK cells as Innate lymphoid cells (ILCs) are the first line of immunity against microbial infection as well as tumor cells and in some situations promote tumor growth [51,52]. Furthermore, NK-DC interaction induces activation and maturation of both [53]. Nevertheless, there has been reported in SARS and SARS-CoV-2 patients NK cell and also NKT cells population were reduced and NKG2A (NK cells inhibitory marker) increase while activation markers such as CD107a, TNF-a and IFN-γ were decreased [11,54,55]. In vitro study on lung epithelial cells transfected with spike protein, 1 (SP1) and co-cultured with NK cells reveal that NK cell-reduced degranulation and increased inhibitory receptor NKG2A/CD94 on NK cells when SP1 was expressed in lung epithelial cells [56]. It seems that the virus hijacks lung epithelial cells and manipulated them to express HLA-E as well as SP1 to exhaust NK cells. Moreover, in systemic inflammation or cytokine storm, IL-6 and IL-10 levels elevated that impaired NK and NKT cells cytotoxicity by inhibiting NKG2D signaling which is important for the elimination of infected cells [57,58] (Fig. 2).

MANIPULATING DENDRITIC CELLS AND T CELLS RESPONSES

After viral infection and the recruitment of immune cells to respiratory tissues, increasing the lungs' lymphocyte population acts as a loop. This phenomenon results in increasing chemotaxis of more lymphocytes [59]. Previous research on SARS-CoV has shown that uptake of the virus by dendritic cells (DCs) is not mediated by ACE2 and other molecules involved in virus entry to cells [60]. Once the virus enters DC, it is expected to break antigen fragments and be present to T cells. But the story does not happen as we expected. The virus enters DC mostly through the DC-SIGN receptor (CD209) [60,61,62]. In contrast to nature, infected dendritic cells produce fewer antiviral cytokines (IFN-α, IFN-β, IFN-γ, and IL-12p40) [62,63,64] (Fig. 2).

On the other hand, the virus replication is limited, and it seems the virus hijacks DC as a cover to escape from the immune system. According to studies, SARS-CoV did not induce apoptosis or maturation of DCs [65]. The virus induces inflammatory chemokines MIP-1α, RANTES, IP-10, and MCP, increasing monocyte/macrophages' migration and T cells to the lung. T cells infected *via* CD147 surface receptor [66,67]. Besides, viral TLRs are not activated in DCs but upregulated chemokine gene receptors (CCR-1, CCR-3, CCR-5). However, research has shown that infected cells have a significant increase in TRAIL gene expression, the phenotype of Killer DC [65]. This phenotype plays a critical role in removing infected T and NK cells and tolerance induction [68]. The TRAIL gene expression has been reported in DCs infected with HIV and macrophages with influenza [65]. Thus, the virus appears to be trying to kill other immune cells (T and NK) and induce immunodeficiency using the infected DCs to facilitate the spread of infectivity. Clinical trials in SARS-CoV-2 patients show the same pattern with defects in DCs maturation and expression of the CD86 molecules. DCs isolated from acute-phase patients, functionality impair to activate T cells and induce clonal expansion against SARS-CoV-2 [69].

The study of experimental DC infection with SARS-CoV helps to elucidate the possible polarization of the immune responses. According to the results, immature dendritic cells change their expression of MHC I, II, CD80, CD86, CD40 molecules due to virus infection [69]. The virus does not replicate in dendritic cells and disrupts the expression of the MHC-I molecule. As a result, the activation of CD8+ cells is eliminated [70]. In addition, the expression of MHC-II, CD80, CD86, CD40 were low and impaired activation of CD4+ T cells. [71,72,73] (Fig. 2). Contrary to the previous findings that confirmed the non-production of IFN I [49,74], dendritic cells produce IFN-α after infection. Still, this cytokine release is too late (24 to 48 h after infection). Based on the 6-hour replication cycle virus in the cell, like influenza, the virus has enough time to complete cell infectivity [49,71,75,76]. However, reports have shown a population of T CD4+, CD8+ cells specific for protein N in patients with SARS-CoV-2 [77,78].

Bret *et al.* showed that patients who recovered from SARS possess long-lasting memory T cells reactive to the N protein of SARS-CoV 17 years after the SARS outbreak. These T cells displayed strong cross-reactivity to the N protein of SARS-CoV-2 [77]. Therefore, it can be concluded that defects in dendritic cell function and subsequent reduction of lymphocytes, especially T cells, are the main features of SARS-CoV-2 infection, which can be identified from the mild phase of the disease [79]. Continued inflammation and lymphocyte proliferation reduction, helping the virus spread and may cause serious tissue damage to the respiratory system, lymph nodes, and bone marrow, as seen in end-stage patients [80].

MANIPULATING B CELLS RESPONSE

The humoral immune response is crucial for the clearance of cytopathic viruses and has a significant role in the immunological memory that prevents reinfection. SARS-CoV-2 evokes a significant B cell response, as evidenced by the detection of virus-specific IgM, IgG, IgA antibodies, and viral neutralizing IgG antibodies (nAbs) days after infection [81].

The seroconversion occurs in most COVID-19 patients between one to two weeks after the onset of symptoms, and antibody titers levels persist in the weeks after virus clearance [82,83]. Antibodies with the ability to bind to the SARS-CoV-2 internal N protein and the external S glycoprotein are detected [84]. The receptor-binding domain (RBD) of the protein S is highly immunogenic. So, antibodies binding this domain can be potently neutralizing,

blocking virus interactions with the host entry receptor, ACE2 [85]. Anti-RBD nAbs detected in most tested patients [86,87].

Antibody responses in patients with COVID-19 co-occur with T follicular helper cell (Tfh) responses. According to reports, a subset of patients may not develop long-lasting antibodies to SARS-CoV-2. It remains unknown whether these patients are vulnerable to reinfection or not [88,89]. This may be due to the small size or absence of germinal centers in thoracic lymph nodes and spleens in patients as well as dysfunction of Tfh cells [90]. Researchers reported the same B cells response in HIV patients, circulating and memory B cells loss during infection even against other bacteria and viruses [91].

The convalescent blood serum samples have been applied with apparently acceptable clinical results in SARA-COVID-2 patients [92]. Until now, the required specific titer and specificity of the antibody repertoire for protection remain undefined [93,94].

Controversially, studies in animal models showed that neutralizing antibodies to S protein could severe lung injury by inflammatory responses [95]. A correlation has been observed where ARDS development coexists with COVID-19 antiviral IgG seroconversion in 80% of patients. Patients who developed neutralizing antibodies to the protein S earlier in infection had a higher disease rate; it took an average of two weeks for patients who died of infection to reach their peak levels of neutralizing antibody activity instead of three weeks for patients who went on to recover [97,98] (Fig. 2).

Even though these indications of a successful neutralizing response in most of the individuals, but higher antibody titers are associated with more severe clinical cases [73,99,100], suggesting that a strong humoral response alone is not sufficient to prevent severe disease. These results were also observed in the previous SARS-CoV-1 epidemic, where neutralizing titers were significantly higher in deceased patients than patients who had recovered [97]. The virus uses antibody response to pulmonary pathology *via* antibody-dependent enhancement (ADE). This phenomenon is recorded when non-neutralizing virus-specific IgG facilitates virus particles' entry into Fc-receptor (FcR) expressing cells, particularly monocytes and macrophages, leading to inflammatory activation of these cells [101]. A study in SARS-CoV-1 on infected rhesus macaques reported that anti-S IgG contributed to severe acute lung injury and massive accumulation of macrophages and monocytes in the lung [95]. ADE was also reported with a monoclonal antibody isolated from a patient with MERS-CoV [102]. Until now, there is no clear explanation for these controversial results of antibody response in CoV patients. Maybe time is the decisive factor in the determination of antibody response as a friend or foe. Probably when the humoral immune response has more than two weeks to complete the maturation process *via* T CD+4 interaction, the formation of germinal centers that and somatic hypermutation, the result is a protective humoral response. But if this branch of adaptive immune response is forced (by hyperinflammatory responses) to act in less than three weeks, the result could be disastrous.

CONCLUSIONS

Due to the obvious unpredictable effect of coronavirus infections, particularly SARS-CoV-2, on human societies, a better understanding of different aspects of the immune responses associated with SARS-CoV-2 infection is required to resolve this crisis. Although, today we have to know how the immune response shapes against viral infections but in some viruses such as SARS-CoV-2, the immune response trend is different due to the behavior of the viruses [103]. Thus, infection of immune cells, hijacking and dysregulation of the cells, inflammation and depletion of DCs, T cells, NK cells, NKT, Tfh, B cells which are finally lead to immunocompromised and facilitate viral spread. Therefore, an effective and regulated immune response at the early infection is important for targeting the virus and controlling the disease progress but when the disease begins to progress, the immune response broadens and becomes potentially more harmful than direct viral damage. Overall, the review suggests further studies on the immune response to SARS-CoV-2 are required, including investigating healthy versus hijacking, manipulating and dysfunctional innate and adaptive immune response determinants that could be an information source for future research on antiviral treatment of COVID-19.

List of Abbreviations

COVID-19: Coronavirus Disease 2019
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
Acute Respiratory Distress Syndrome (ARDS)
Coronaviruses (CoVs)
Human Immunodeficiency Virus Type 1 (HIV-1)
East Respiratory Syndrome Coronavirus (MERS-CoV)
Angiotensin-converting Enzyme 2 (ACE2)
Interferon Regulatory Factor (IRF)

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