Chapter

Immune Response to COVID-19

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Abstract

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) invades the host's cells via the angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2). ACE2 and TMPRSS2 molecules are highly expressed on the respiratory tract but are also expressed in other organs such as kidneys, heart, and intestine, which could partially explain the multiple organ infection, damage, and failure. During the COVID-19 disease course, patients may develop a dysregulation in the immune response, with an exacerbated production of pro-inflammatory molecules and hypercoagulation, which can collaborate to the increase in tissue damage and death. This chapter will cover general aspects of the innate and adaptive immune response during COVID-19, the impact of comorbidities on the immune response to SARS-CoV-2, and the immune response generated by COVID-19 vaccines.

Keywords: SARS-CoV-2, COVID-19, immunology, immune response, inflammation

1. Introduction

SARS-CoV-2 has four main structural proteins: the spike protein (S protein), the nucleocapsid protein (N protein), the matrix protein (M Protein), and envelope protein (E protein) [1, 2]. The SARS-CoV-2 infection starts when the virion enters the host's cell, through the connection between the viral S protein and the ACE2 receptor and TMPRSS2 on the host's cells, similarly to severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) [3].

ACE2 and TMPRSS2 are highly expressed in the lungs, partially explaining the high incidence of respiratory disorders. Nevertheless, ACE2 and TMPRSS2 are expressed in many other different organs in the human body, such as the brain, heart, liver, kidney, colonic epithelial cells, intestine luminal cells, and small intestinal enterocytes [4], with reports of SARS-CoV-2 infection on multiple organs [5]. In addition, SARS-CoV-2 may generate a systemic and exacerbated inflammatory response named "cytokine storm", which can lead to viral sepsis [6].

Several systemic biomarkers have been associated with the progression of the disease, such as creatinine, urea, C-reactive protein, ferritin, lactate dehydrogenase, and D-dimers in the blood, increase in the neutrophil-to-lymphocyte ratio, and reduction in platelet count in the blood [7–15]. During COVID-19 the increase in blood levels of chemokines and cytokines increases the pro-inflammatory stimulus and recruitment of immune cells to the infection site. Several risk factors contribute to the disease's severity, such as comorbidities and co-infections [16–18] In this chapter, the current knowledge about the innate and adaptative immune response during COVID-19 and the influence of comorbidities will the reviewed.

2. Innate immune response to SARS-CoV-2

Upon infection by SARS-CoV-2 several chemokines (CCL2, CCL3, CCL4, CCL5, CXCL8, CXCL9, and CXL10) and pro-inflammatory cytokines (IFN-γ, TNF, IL-1, IL-6, IL-12) are released, these molecules will induce cell activation, migration, and infiltration of the infected tissue by innate immune cells like monocytes and neutrophils and further activate local cells such as resident macrophages [19]. These cells will further increase the local production of pro-inflammatory mediators, which could result in tissue damage, such as alveolar damage, formation of edema, and reduced lung capacity. In addition, cytokines can generate a systemic effect, resulting in damage to other organs (kidney, liver, spleen, among others) [20]. An increase in circulating pro-inflammatory monocytes and nonclassical monocytes are commonly observed in COVID-19 patients [21, 22].

Concomitantly, the number of neutrophils in the blood increases, and the infiltration of neutrophils to the infected tissue. Upon infiltration, neutrophils release inflammatory mediators, cytokines, and neutrophil extracellular traps (NETs) which can further increase tissue injury and cellular death [23, 24]. The local production of pro-inflammatory factors, viral particles, and cellular death induces the activation of macrophage and dendritic cells (DCs), which will further increase the production of cytokines and chemokines and antigen presentation [20, 25] DCSs are commonly referred to as professional antigen-presenting cells (APCs) and integrate innate and adaptive immune response. In COVID-19 they can uptake SARS-CoV-2 viral particles, be activated, migrate to lymphatic tissue, initiate antigen presentation, and trigger adaptive immune response. Nevertheless, DCs can also be infected by SARS-CoV-2 [26], reducing quantitatively, generating functional impairment, and lower lymphocyte immune response [27].

The complement system has also been implicated in the pathogenesis of COVID-19. The activation of C3 and C5 complement components are correlated with disease severity and lung biopsy from severe COVID-19 patients presented high C3-fragment content [28]. C3-deficient mice are partially protected from respiratory dysfunction after SARS-CoV-1 infection, exhibiting less inflammatory infiltrate in the lungs, reduced production of cytokines and chemokines, but similar viral load in the lung tissue as Wild Type mice [29]. Importantly, treatment with anti-C5a antibodies resulted in clinical improvement in COVID-19 patients [28]. Indicating a possible use of complement-inhibitor to ameliorate lung injury in COVID-19 patients.

The role of eosinophils and basophils in COVID-19 is yet to be fully comprehended. To the moment, a negative correlation is established between circulating eosinophil and basophil count and COVID-19 severity, with patients exhibiting an increase in those cells upon SARS-CoV-2 clearance [30, 31]. Mast cells (MCs) may also play a role in COVID-19, since they can be activated by viral products and release chemokines, cytokines, and inflammatory mediators, increasing vascular permeability and cellular infiltrate [32]. A few reports have indicated that COVID-19 inflammatory syndrome is in many aspects similar to Mast cell activation disease [32, 33].

The frequency of mononuclear and polymorphonuclear myeloid-derived suppressor cells also increases in the blood, but not in the lungs, of COVID-19 patients according to the severity [15, 34]. Importantly, these cells do maintain their immunosuppressive functions in COVID-19 patients [35].

The hyperinflammatory state is also accompanied by a dysregulated anti-inflammatory state, with an increased early IL-10 production, which could curb the anti-viral immune response [36], and impaired T cells (CD4+ and CD8+) and T regulatory cells function [37].

3. Adaptive immunity in COVID-19

Patients with moderate and severe COVID-19 commonly present a reduction in circulating lymphocytes (T cells, B cells, natural killer cells). T CD4+ and T CD8+ cells are reduced in moderate COVID-19 patients and further reduced in more severe patients, with or without a significant change in CD4+/CD8+ ratio [38, 39]. A few reports have identified patients with a specific reduction in CD8+ cells, which is associated with poor prognosis [38]. The reduction of B cells and innate lymphocytes, like NK cells, has also been reported, but to the moment are not currently associated with severity or prognosis [40].

The mechanism for the reduction in lymphocytes is still under investigation, several reports indicate that exhaustion and apoptosis may be the primary causes of lymphopenia [41], and one report indicating direct lymphocyte infections by SARS-CoV-2 [42]. Due to the central role of lymphocytes on anti-SARS-CoV-2 immune response, several interventions to modulate the T cell proliferation or apoptosis are also being investigated [43].

Although the reduced T cell count in the blood of COVID-19 patients may reflect the recruitment to infected tissue or be influenced by the use of steroid treatment to curb the inflammation, some studies have also reported significant T cell reduction in secondary lymphoid organs of patients infected with SARS-CoV-2 [44].

Even with the reduction in lymphocytes, T cell receptor analysis indicated that COVID-19 patients do present an increase in SARS-CoV-2-specific T-cells [45]. Proliferation markers, such as Ki67, and activation markers, such as CD28 and HLA-DR, are increased in both CD4+ and CD8+ cells, including activated, effector, and memory T-cells, in COVID-19 patients in comparison to recovered patients and non-COVID-19 patients [46]. Several reports identified an increased expression of exhaustion and inhibition-associated markers in circulating T cells such as CD39, CTLA4, LAG3, NKG2A, PD-1, and TIM3 [47].

In summary, these results indicate an expansion and overactivation of CD4+ and CD8+ T-cells that could lead to unresponsiveness or cell death. This appears to be true since even with a highly activated profile, CD8+ T cells from COVID-19 patients have a reduced cytokine production after in vivo stimulation [41].

CD4+ T cells may have a dual role in COVID-19, reports have identified that patients with higher activation markers on CD4+ cells have a poor prognosis, and others have identified that patients with higher T helper 1 profile (Th1) present a less severe disease [46, 48]. SARS-CoV-2-specific Th1 cells have been identified, but patients with profiles associated with SARS-CoV-2-specific Th2 and Th17 response have also been identified [49]. Another investigation has also identified an increase in transforming growth factor-β (TGFβ)-producing T cells in COVID-19 patients [50]. CD4+ FOXP3+ T regulatory cells increase during the disease but suffer a reduction in critically ill patients, which could corroborate the hyperactivation of the immune system [47, 50].

3.1 Antibodies and B CELLS

The Production of Antibodies, especially SARS-CoV-2-specific IgM and IgG, have been used as a diagnostic tool for COVID-19, although the presence of virus-specific IgG antibodies does indicate viral clearance [51]. Anti-SARS-CoV-2 antibodies may block and neutralize SARS-CoV-2 and prevent COVID-19 development.

Importantly, reports have identified that asymptomatic, moderate, and severe COVID-19 present different IgM and IgG production courses and may vary in quantity. Severe COVID-19 patients produce anti-SARS-CoV-2 IgG earlier in comparison

to moderate patients, and asymptomatic and mild patients produce less neutralizing antibodies in comparison to moderate and severe COVID-19 patients [52].

More importantly, serum antibody titers rapidly decay after COVID-19, with conflicting reports with antibody titers decaying after a few months post-diagnosis [53, 54]. Nevertheless, antigen-specific memory B cells [55], T cells, and other components of the immunological memory remain effective and can be detected in convalescent patients [52, 56]. As memory cells can rapidly respond upon subsequent antigen encounter (infection), some degree of long-term immunity is expected [57].

Since SARS-CoV-2 S protein is necessary for the infection, neutralizing antibodies against this protein could in theory prevent the infection [2]. Both S-protein and N-protein specific IgM and IgG increase after the infection by SARS-CoV-2 [58], with S-protein IgG having a negative correlation with inflammatory markers in COVID-19 patients [58].

COVID-19 patients present a rapid increase in SARS-CoV-2-specific IgM, IgA, and IgG, commonly observed around a week after the infection [51, 59], however, comorbidities may impact not only on the inflammatory response during COVID-19 but also antibody production, reports identified patients with human immunodeficiency virus (HIV) presenting a delayed SARS-CoV-specific IgM and IgG production [60, 61].

4. Comorbidities and severe COVID-19

Several comorbidities have been described as risk factors for the progression of COVID-19 into a severe, critical, and lethal stage. The first reports have identified advanced age, systemic arterial hypertension, and Diabetes Mellitus with a higher hospitalization and severity for COVID-19 patients [62–64]. Comorbidities may influence COVID-19 severity via an increase in pro-inflammatory response, coagulatory disorders, or different ACE2 expression [65–67]. Investigations confirmed that old age, systemic arterial hypertension, Diabetes Mellitus [68], obesity [16], alcohol consumption [69], smokers and chronic obstructive pulmonary disease (COPD) [70], heart disease, liver disease and kidney disease [71], cancer [72, 73], immunodeficiencies, transplanted patients [74], and co-infections [17, 74] are in fact risk factor for severe COVID-19 and increase death risk and the presence of two or more comorbidities further increase the death risk [75]. We will review the impact of the most common comorbidities associated with poor COVID-19 prognosis and their influence on the anti-SARS-CoV-2 immune response.

4.1 Old age

The majority of the fatal cases of COVID-19 occurred in elderly individuals [76, 77]. Several facts may explain this phenomenon, such as the accumulations of other comorbidities, immunosenescence, and inflammaging.

Immunosenescence is defined as a decline in the immune system function, characterized by the reduction in qualitative and quantitative responses to infections, neoplasia, and vaccination [78]. With age, the production of naïve lymphocytes (T and B cells) is reduced, and the function of innate immune cells is weakened, therefore negatively impacting the immune response during infections [78]. Concomitantly, the elderly develop a chronic low-grade systemic inflammation, named inflammaging.

The low-grade pro-inflammatory state is characterized by the increase in serum inflammatory mediators, such as C-reactive protein, IL-1, IL-6, and TNF [79, 80], which is associated with an impaired and dysregulated immune response.

In summary, accumulations of other comorbidities such as systemic arterial hypertension and Diabetes Mellitus, immunosenescence, and inflammaging present in elderly patients are likely to contribute to the poorer outcome in COVID-19 [81].

4.2 Systemic arterial hypertension

Systemic Arterial Hypertension is common among hospitalized COVID-19 patients and is associated with higher severity of the disease and mortality [15, 82, 83]. The initial hypothesis for this was that Systemic Arterial Hypertension and the drugs commonly used for its control, like renin–angiotensin–aldosterone system (RAAS) inhibitors that increase expression of ACE2, increasing the susceptibility to SARS-CoV-2 [68]. However, a recent report has not identified an association between the use of RAAS inhibitors and increased severity or death in COVID-19 patients [84].

Other explanations are related to the modulations of ICAM and E-selectin, which are increased in systemic arterial hypertension and can be downregulated by dexamethasone [85, 86]. Dexamethasone treatment during COVID-19 can reduce the death rate in patients receiving both invasive and non-invasive mechanical ventilation [87]. Although no investigation on the modulation of ICAM and E-selecin has been performed, these results further support that the reduction of inflammation during COVID-19 can improve the patients' outcome [87].

4.3 Metabolic diseases (type 1 and 2 diabetes mellitus and obesity)

Diabetes Mellitus (DM), obesity, and metabolic syndrome increase the levels of circulating pro-inflammatory cytokines in comparison to lean people. This low-grade inflammation is lower than individuals with infections but can influence cellular metabolism and immune response [88, 89]. Obesity affected the frequency and ratio of CD8+ and CD4+ T cells, inducing an increase in inflammatory macrophages [90] and reduces the frequency of T regulatory cells, therefore favoring a more pro-inflammatory profile [91]. In obesity, there is a great increase in memory T cell in the adipose tissue, that upon infection can generate pancreatitis, and increase mortality [92]. Similar to inflammaging, obesity is also characterized by low-grade inflammation, with an increase in the production of chemokines and cytokines by the adipose tissue [92]. Obesity is also associated with several risk factors for COVID-19 such as respiratory dysfunctions, type 2 Diabetes Mellitus (DM2), and hypertension [16].

The type of Diabetes Mellitus is rarely described in COVID-19 investigations [93]. A recent investigation compared the mortality rate among type 1 Diabetes Mellitus (DM1) and DM2 patients during SARS-Co-V-2 infection. The unadjusted mortality rate per 100 000 was 27 for non-DM, 138 in DM type 1 (DM1) and 260 in DM2, the adjusted data verified that the odds ratios of COVID-19-related deaths were 3.51 in DM1 and 2.03 in DM2 [94]. Concluding that both DM types present a greater risk of death by COVID-19 [94].

An important factor is that poor glycemic control can influence the disease course [95], this is supported by several manuscripts that described the deleterious effect of elevated blood glucose levels on the immune response to COVID-19 and DM2 patients with better glycemic control presented a lower death rate in comparison with COVID-19 DM2 patients with hyperglycemia [96–98]. Diabetic patients

also present a low-grade inflammation with an increase in pro-inflammatory cytokines and reactive oxygen species, but an impaired inflammatory response to microbial products [99, 100].

Non-diabetic patients with COVID-19 can also present hyperglycemia [15], and is associated with an increased incidence of severe illness and death risk [101]. Several drugs used for the control of inflammation can modify or induce hyperglycemia during COVID-19 hospitalization [102], which could affect the anti-SARS-CoV-2 immune response. A few manuscripts have hypothesized COVID-19 causes alterations of glucose metabolism, via direct SARS-CoV-2 infection of the pancreatic beta cells [103, 104]. Importantly, metabolic alterations have been described in COVID-19 patients, with and without DM, developing ketosis and ketoacidosis [105]. In a case report, a 29 years old patient, non-DM with a normal glucose level was diagnosed with COVID-19. Two weeks after recovered from COVID-19 was diagnosed with DM1 [106].

Therefore, COVID-19 may also represent a risk factor for the development of DM. A related point to consider is that DM patients may have long-term consequences from COVID19, with an increase in the need for daily insulin [107]. Currently, there is no explanation for this phenomenon, but COVID-19-mediated gastrointestinal dysbiosis could be a factor since the microbiota can influence the development or aggravate metabolic disorders [108]. Also, metformin, a drug commonly used by DM2 patients, may cause alteration on the gut microbiota and impact their anti-SARS-CoV-2 immune response [109, 110].

4.4 Chronic obstructive pulmonary disease (COPD), smoking, and other respiratory disorders

Chronic obstructive pulmonary disease (COPD) affects millions of people worldwide. COPD is characterized by progressive and irreversible airflow limitation due to structural alterations on the small airways. Smoking is the leading cause of COPD, due to the increase in inflammation and pulmonary remodeling [111]. Smoking and COPD are known to increase the risk for respiratory infections [112, 113]. Smokers and COPD patients have been identified among hospitalized COVID-19 patients since early reports [83]. COPD and smoking have been associated with an increased incidence, severity, and poor prognosis in COVID-19 [70, 114–116].

A common component in tobacco cigarettes and electronic smoking devices is nicotine, which can downregulate Interferon regulatory factor 7 and curb antiviral immune response [117]. COPD patients have a reduction in the expression of type I and type II interferons, and interferon-stimulated genes, therefore having a reduced antiviral response resulting in frequent respiratory exacerbations [118].

Other mechanisms postulated for the increase in susceptibility among those patients are the increase in lung inflammation and oxidative stress [119] and increase in the expression of the ACE2 receptor, SARS-CoV-2 entry receptor, in COPD and Smokers [120].

Interestingly, allergic asthma characterized by a Th2 immune response, with increased production of IL-4, IL-5 and IL-13, is associated with a reduction of the expression of ACE2 receptor [65]. And asthma is associated with a reduction in the severity of COVID-19 [121, 122]. It is important to highlight that non-allergic asthma or neutrophilic asthma increases the production of IL-17 in the lungs, which increases ACE2 expression, therefore possibly increasing the risk for severe COVID-19 [123].

Other respiratory diseases such as bronchiectasis, sarcoidosis, idiopathic pulmonary fibrosis, and lung cancer are also associated with an increase in COVID-19 severity, but further investigations are needed to understand the immune mechanism [124].

Since asthma, smoking and COPD are also commonly associated with other comorbidities, this could further increase the COVID-19 severity and death risk in these populations [125, 126].

4.5 Neoplasia (cancer)

Cancer patients are regarded as more vulnerable to severe COVID-19, due to the direct immunosuppression caused by the tumor or indirectly by the antitumor treatment [127, 128]. Patients with hematological malignancies, such as leukemia and lymphoma, have an exacerbated cellular proliferation with a reduction in the immune response, increasing the susceptibility to infections [129].

Location and cancer stage can also impact COVID-19 development. A recent report among patients with cancer identified that lung cancer, gastrointestinal cancer, and breast cancer are the most common [130]. Patients with stage IV cancer also account for a high number of COVID-19-infected patients [130, 131]. Cancer patients with COVID-19 also have an increase in hospitalization duration and severity [130, 131].

In addition to immune suppression, hospitalized cancer patients or patients undergoing frequent hospital visits may be at great risk for SARS-CoV-2 infection, increasing the necessity for precautionary measures [132, 133].

4.6 Immunodeficiencies

Immunodeficiencies are uncommon and chronic disorders of the immune system, that hinders the ability to develop an appropriate immune response, leading to deficient, exacerbated, or absent response to an infection or disease [134]. The immunodeficiency can be localized in any cell or structure of the immune system, compromising barrier immunity, innate immunity, or adaptive immune.

Immunodeficiency disorders can be divided into primary and secondary immunodeficiencies. Primary immunodeficiencies are a consequence of genetic defects, and secondary immunodeficiencies are caused by external or environmental factors, such as nutritional disorders or HIV [135].

The most common primary immunodeficiency is the common variable immunodeficiency that affects the patients' ability to mount an appropriate humoral response during infection [136]. These patients are commonly treated with immunoglobulin replacement [137]. A recent case report identified a patient with common variable immunodeficiency and severe COVID-19, that was successfully treated with COVID-19 convalescent plasma [138]. Although it is important to highlight that convalescent plasma treatment has controversial results, even when applied at the beginning of the infection and with high titers of neutralizing antibodies [139–141].

Reports of patients with primary and secondary immunodeficiencies identified an increase in severity and mortality due to COVID-19 in these patients in comparison with available data on COVID-19 [142, 143]. Also, patients with immunodeficiencies can present other comorbidities, further increasing the death risk by COVID-19 and increased risk for the development of secondary infections during hospitalization [142, 143]. Certain immunodeficiencies compromise specific anti-viral immune responses, for example, TLR7 gene defect, with compromised type I and II interferon production, are linked to severe COVID-19 in young individuals [144].

A common secondary immunodeficiency AIDS, the one caused by HIV, can compromise the anti-viral immune response during COVID-19. Patients with low CD4+ count have a higher severity and mortality risk compared with patients with normal CD4+ count [145]. In patients with HIV viral suppression, other comorbidities may increase patients' death risk during COVID-19 [30, 145].

4.7 Co-infections

Bacteria and viral co-infections and secondary infection in COVID-19 patients are important factors in the patients' treatment and outcome [146]. Co-pathogens included bacteria, fungi, parasites and viruses can modulate patients' immunity and also curb the anti-SARS-CoV-2 immune response [146]. Patients with invasive mechanical ventilation are at greater risk for bacterial co-infections [17, 147], also several patients report diarrhea without gastrointestinal SARS-CoV-2 infection, which could be a secondary gastrointestinal infection or microbiota dysbiosis [108].

Co-infections can increase the susceptibility to severe COVID-19, by an increase in the hyper inflammation or hypercoagulation status [74, 148]. Few reports have investigated the impact of parasites on COVID-19, such as leishmaniasis, toxoplasmosis, malaria, and Chagas disease [148–151]. Clinical manifestations of those diseases are usually associated with an increased and unregulated type 1 pro-inflammatory response, similar to COVID-19 [151]. In fact, a few case reports identified that chagasic patients with COVID-19 present an exacerbated inflammatory response, with a high lethality [74, 148]. This represents a further difficulty in the treatment of COVID-19, since the combination of drugs for the treatment of COVID-19 and the co-infections, the immune response to the co-infections and possible comorbidities need to be equated.

5. COVID-19 vaccines

COVID-19 vaccines are currently the only prophylactic/curative treatment for COVID-19, since drug repurposing and monoclonal antibodies trials had limited success, and investigations with convalescent plasma have conflicting results [87, 139–141, 152, 153]. Several vaccines are currently developed and in developing. Due to the high demand for a COVID-19 vaccine, significant advances in vaccine technologies have been made in the last year. Currently, 3 types of vaccines are being administered worldwide: inactivated virus vaccines (IVV) [154], vaccines that use mRNA with lipid nanoparticle (LNP) delivery systems [155], and vaccines containing DNA delivered within non-replicating recombinant adenovirus (AdV) vector systems [156]. AdV and mRNA vaccines aim to induce the production of SARS-CoV-2 S protein and induces the production of neutralizing antibodies [139, 141, 153].

All vaccines can induce the recognition of the viral antigen (immunogen) and also serve as an adjuvant to boost the immune response, the immunogen is recognized by innate immunity receptors such as toll-like receptors 3 and 7, RIG-I, and NOD2 inducing cellular activation and the production of interferons. This process will also induce the migration of DCs to secondary lymphoid organs and prime SARS-CoV-2-specific T cells [139, 141, 153]. Further questions regarding the effectiveness of vaccines are still going to be investigated, especially the long-term immunity and efficacy against new variants.

6. Conclusions

COVID-19 is a hyperinflammatory and hypercoagulation syndrome, with a hallmark increase in inflammatory mediators such as C-reactive protein, creatinine, urea, cytokines, and chemokines in the blood, with an increase in the neutrophil count and reduction in lymphocyte and platelet count. These processes lead to a

dysregulated immune response that can be lethal. The overall mortality ratio is still unknown but is higher in patients with comorbidities. Patients with common and rare comorbidities may present differences in the immune response in comparison to healthy individuals.

The COVID-19 pandemic is a hallmark of world history, this systemic disease killed millions, raised ethical dilemmas, and put science and immunology on the daily lives of millions worldwide. Immunological investigations have helped the development of treatments and vaccines for this disease, but many questions are still left to be answered. The current knowledge is limited, but never in the previous history so many researchers around the world were focused on investigations on one disease. Several technologies developed and tested during this pandemic may bring light to other diseases, such as the new technologies in vaccine development and treatments.

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