Innate Immunity and SARS-CoV-2 Infection

Subjects: Immunology

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The innate immune system is important for initial antiviral response. SARS-CoV-2 can result in overactivity or suppression of the innate immune system. A dysregulated immune response is associated with poor outcomes; with patients having significant Neutrophil-to-Lymphocyte ratios (NLR) due to neutrophilia alongside lymphopenia. Elevated cytokines like interleukin (IL)-6 and IL-8 leads to overactivity and is a prominent feature of severe COVID-19 patients. Several factors like pre-existing co-morbidities, genetic risks, viral pathogenicity, and therapeutic efficacy act as important modifiers of SARS-CoV-2 risks for disease through an interplay with innate host inflammatory responses. In this review, we discuss the role of the innate immune system at play with other important modifiers in SARS-CoV-2 infection.

Keywords: SARS-CoV-2 ; COVID-19 ; innate immunity ; cytokines

1. Introduction

Pandemics are a serious global health concern that demonstrate how interconnected the world has become. Coronaviruses are enveloped, positive-sense, and single-stranded RNA viruses known to cause disease in mammals and birds, with human endemic strains causing minor upper respiratory infection in immunocompetent individuals [1][2]. Similar to its novel CoV epidemic predecessors, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 is in the genus betacoronavirus and is of zoonotic origin, which frequently causes upper and lower respiratory infection with potentially life-threatening complications [1][2][3][4]. Critical patients can develop acute respiratory distress syndrome (ARDS), a hyperinflammatory lung disease, and require prolonged mechanical ventilation and intensive care.

SARS-CoV-2 was declared a pandemic by the World Health Organization (WHO) on 11 March 2020 after it had spread throughout the world, transmitted by respiratory droplets and person-to-person contact [5]. As of 2 June 2021, over 170 million confirmed cases and over 3.55 million confirmed deaths have been reported worldwide [5]. COVID-19 is less lethal than SARS-CoV or MERS-CoV based on case fatality rates but more communicable overall, and thus exceeded these CoV in both total cases and deaths in a relatively short period [6]. Patients with SARS who recovered later showed some degree of pulmonary fibrosis [7], which causes concern for the potential long-term impact of COVID-19.

The vast majority of confirmed patients in China with COVID-19 experienced mild disease with symptoms of fever, dry cough, and fatigue, but 14% of cases were classified as severe with symptoms of dyspnea and low blood oxygen saturation, and 5% as critical with symptoms of respiratory failure, septic shock, or multiple organ failure (5). The case fatality rate was 2.3% for all COVID-19 patients, but death occurred only in critical cases with a subsequent fatality rate of 49% [4]. Deaths were associated with older age and pre-existing comorbidities [4], both of which contribute to an overall weaker immune response.

Currently there exists no definitive therapeutic treatment for COVID-19 and care is largely supportive and experimental while relying on the patient's own immune system to clear the virus. A crucial component of an effective antiviral immune response is in the innate immune system, which can hinder viral replication while removing infected cells during the onset of disease and potentially resolve an infection during an early phase with a robust effort. The innate immune system is an essential initial response to infection by a pathogen, and patients whose systems fail to respond efficiently during the onset may have problems containing it later.

The complexities regulating immune competency is vast, consisting of individual and environmental inputs. Here, we present an integrated framework (for example, genetic risks, pre-existing co-morbidities, viral pathogenicity, and therapeutic efficacy) at play as important modifiers of SARS-CoV-2 risks for disease through an interplay with innate host inflammatory responses. Specifically, an understanding of these and other complex relationships will provide important

insight into how alterations in the innate immune response in severe COVID-19 caused by SARS-CoV-2 would inform new therapies and treatments that mitigate viral replication as well as overactive inflammation created by the innate immune systems.

2. SARS-CoV-2 and COVID-19 Pathogenesis

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) , a causative agent of coronavirus disease 2019 (COVID-19), the severe respiratory illness that is now rampaging the world, is an enveloped, single positive-strand RNA virus [8]. The envelope consists of a lipid bilayer derived from the cell membrane of the host and four structural proteins, spike (S), envelope (E), membrane (M), and nucleoprotein (N), as well as variable number of nonstructural proteins.

The most common route of transmission of SARS-CoV-2 is via infectious respiratory droplets and person-to-person contact. Likely portals of infection include the conjunctival epithelium, the nasal epithelium, and inhalation via the mouth. Patients who experience repeated exposures, such as healthcare workers, are more likely to develop severe disease [9]. SARS-CoV-2 replicates extensively in the bronchial epithelium, which could help explain the high levels of transmission [10].

SARS-CoV-2 primarily enters human cells through the angiotensin-converting enzyme 2 (ACE2) receptor although other routes of entry of the virus cannot be excluded [11][12][13]. ACE2 counteracts the effects of angiotensin II and helps regulate vascular tone and importantly for SARS-CoV-2, alveolar secretion of angiotensin II in the lung [14]. ACE2 is expressed in many different cell types, including the nasal and alveolar epithelium, the heart, the blood vessels, and the kidneys [15][16]. Daly et al. showed that a component of SARS-CoV-2 S protein binds to cell surface neuropilins (NRP1 and NRP2) via the S1 CendR motif generated by the furin cleavage of S1/S2, which could be a potential therapeutic target [17].

Coronavirus cellular entry is dependent on binding of the spike protein (S) to a specific cellular receptor, followed by S priming by cellular proteases [15][18]. However, TMPRSS2 is not found in all ACE2 positive cells, suggesting that SARS-CoV-2 might use alternative pathways. While TMPRSS2 activity is documented to be important for viral transmission [19] [20], the potential of cathepsin B/L or other proteases to functionally replace TMPRSS2 has not been determined [15]. Mature enterocytes that express high levels of ACE2 receptor were found to be susceptible to SARS-CoV-2 infection with TMPRSS2

Upon entry, the infected SARS-CoV-2 is known to encode a polyprotein proteolytically processed into 16 nonstructural proteins (Nsp1–16) from open reading frame (Orf) 1a/b, structural proteins including S, E, M, and N, and 9 accessory proteins from Orf3a, 3b, 6, 7a, 7b, 8, 9b, 9c and 10 [21][22]. Viral gene and the expressed proteins in the infected cells then trigger the host immune responses, and the innate immune cells initiate an inflammatory cascade. However, the signaling mechanisms responsible for induction of inflammatory cytokines by SARS-CoV-2 has not been fully elucidated.

3. Innate Immune Cells & Their Role in COVID-19

Many components of the innate immune system are important for initial detection and clearance of viral infections. Another notable clinical feature is that the severity of the disease among infected patients range from asymptomatic to symptomatic, and even among the symptomatic patients, approximately 80% of the infected patients show mild symptoms, whereas 15% of the confirmed cases progress to the severe phase. Finally, as noted previously, the elderly and those with co-morbidities, such as diabetes, obesity and cardiovascular, respiratory, renal, and lung diseases, are the most susceptible to COVID-19 and its severe disease complications. Lucid understanding of the clinical immune response variances for SARS-CoV-2 is therefore imperative in combating COVID-19.

Upon virus entry into the cell cytoplasm via endocytosis, antiviral innate immune signaling pathways in the virus-infected host are activated to thwart virus replication [23]. Cytokines secreted by the activated innate immune system then stimulate the adaptive immune responses, recruit various immune cells to the site of infection, and help to inhibit viral replication. These macrophages, along with neutrophils, phagocytose infected cells and pathogens. The complement system also participates in immune cell recruitment, activation, and ultimately destruction of pathogens.

Type I interferons are among the first cytokines to be upregulated in virus-infected cells and are important in coordinating the antiviral response and inflammation [41]. However, the IFN system is generally significantly suppressed in most severe SARS-CoV-2 patients [42]. Schroeder et al. showed that SARS-CoV-2 suppresses cytokine induction and interferon signaling with lower efficiency than SARS-CoV, despite the shared genome architecture and expression of homologous viral proteins [24]. Whole exome or genome sequencing in patients with life-threatening COVID-19 pneumonia

revealed that inborn errors of TLR3- and IRF7-dependent type I IFN immunity could underlie life-threatening COVID-19 pneumonia in patients with no prior severe infection [25]. I IFN administration may be of therapeutic benefit in selected patients, at least early in the course of SARS-CoV-2 infection.

Several previous studies have reported an association between dysregulated secretion of cytokines and progression to severe SARS-CoV-2 [26][27]. Patients with severe and critical cases of COVID-19 often have high levels of cytokines including IL-1, IL-2, IL-6, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1α, and tumor necrosis factor-α (TNFα) The overabundance of these cytokines can lead to a “cytokine storm”, which may play a large role in COVID-19 pathogenesis and initiation of viral sepsis and inflammatory-induced lung injury. These patients often develop viral pneumonia, which may progress to acute respiratory distress syndrome (ARDS), or even multi-organ failure [10][28][29][30].

Significant increases in inflammatory cytokines and chemokines in serum levels were seen for severe COVID-19 patients, but it is currently uncertain if it is directly involved in further lung damage [31]. Different analyses have provided a wide array of various elevated cytokines that may potentially lead to local lung inflammation and disease progression. A correlation was shown in another study between increasing disease severity and circulating proinflammatory cytokines, including TNF-α, interleukin-2R (IL-2R), and interleukin-6 (IL-6) [31]. Another found elevated levels of IL-6, IL-1α, CCL2, CCL8, CXCL2, CXCL8, CXCL9, and CXCL16 but low levels of Type I and Type III interferons (IFN)

In a comparison of bronchoalveolar fluid (BALF) samples for moderate and severe patients, severe patients showed increased levels of IL-6, IL-8, and IL-1β and chemokines CCL2, CCL3, CCL4, CCL7, CCL8, CXCL2, CXCL8, CXCL9, CXCL10, CXCL11, CXCL16, FGF, CSF-3, CSF-2, PDGF, and VEGF were also elevated [27][32][33]. Chemokines CCL2, CCL8, and CXCL10 chemically attract monocytes to a location, while CXCL2 and CXCL8 (also called IL-8) is a chemotactic for neutrophils and T cells [32][34]. Recruitment of leukocytes to the lungs is necessary for viral clearance but excessive inflammation can result in fibrosis, poor alveolar gas exchange, and patient deterioration. Lung interstitial tissue showed extensive infiltration from CD4+ T cell, CD8+ T cell, macrophages, and GZMB+ cells [35].

Through the formation of neutrophil extracellular traps (NETs), they can induce IL-1β expression from macrophages which has been shown to cyclically induce further NET formation in some disease states [36]. Blood serum of COVID-19 patients displayed elevated markers indicating NET formation, including citrullinated histone H3 (Cit-H3) and myeloperoxidase-DNA (MPO-DNA), which also was further shown to have activated NET formation in control neutrophils when the COVID-19 sera was applied in vitro [37]. In contrast, deoxyribonuclease I (DNase I) can work to promote the clearance of overproduced NETs and, thus, minimize unwarranted neutrophil-mediated collateral damage [38]. Immunomodulation through activation of the innate immune sensor toll-like receptor 5 (TLR5) that recognizes flagellin could potentially act as a trojan horse “danger” signal, which may trick the host into thinking that immune responses are required to suppress a “bacterial” infection but instead activates antiviral responses to eliminate SARS-CoV-2 [39].

COVID-19 induced sepsis was categorized by Giamarellos-Bourboulis et al. into three classifications: macrophage activation syndrome (MAS), immunoparalysis with downregulation of human leukocyte antigen D related (HLA-DR) on CD14 monocytes, and an intermediate state without apparent immune dysregulation [40]. Patients with severe respiratory failure (SRF) exhibited either MAS, which is associated with elevated levels of IL-1β, or immune dysregulation, which is associated with IL-6 [40]. Approximately, a fourth of COVID-19 patients with SRF had indications of MAS, while the majority had immune dysregulation [40]. All of these innate immune responses lead to a severe hyperinflammation in COVID-19 patients.

To date there has been little evidence of direct infection of monocytes or macrophages by SARS-CoV-2, but studies have shown that SARS-CoV and MERS-CoV infection results in aberrant cytokine production [41]. Only MERS-CoV was capable of active viral replication inside monocyte-derived macrophages (MDM), but both viruses failed to activate antiviral cytokines IFN-α and IFN-β within infected MDM while significantly increasing TNF-α and IL-6 expression [41]. A murine animal model of infected macrophages with the spike (S) protein from SARS-CoV demonstrated the upregulation of TNF-α and IL-6 caused by inducing the NF-κB pathway [42]. This was later confirmed with human peripheral blood monocyte macrophages, where the S protein activated monocytes increased TNF-α and IL-6 along with a significant increase in IL-8 that was dose dependent [43].

Autopsy examination of six COVID-19 patients revealed SARS-CoV-2 infection of the spleen and lymph nodes with extensive damage to its tissues as well as follicle depletion [44]. Viral proteins were found in the spleen and lymph node resident CD169+ macrophages, but not in CD3+ T cells or B220+ B cells, indicating damage was likely macrophage related and SARS-CoV-2 potentially migrated to the locations utilizing infected macrophages [44]. Infected macrophages were reported to have also increased expression of IL-6, a cytokine known to induce apoptosis in lymphocytes and potentially a cause of lymphopenia in COVID-19 patients [44].

SARS-CoV was known to cause lymphopenia in SARS patients with altered lymphocyte subsets [45], but whether that was the result of the viral infection or due to following treatment for inflammation with glucocorticoid steroids has remained uncertain [46]. The exact mechanism is currently unknown for what directly causes the depletion of lymphocytes and resulting lymphopenia in COVID-19 patients. but there is no evidence of actual viral infection of the lymphocyte demonstrated from viral gene expression within the cell [34]. Peripheral blood mononuclear cells (PBMC) have been shown to have increased expression of p53 signaling pathways and cellular apoptosis, which could potentially have been induced from SARS-CoV-2 [34].

Patients with onset of symptoms and blood lymphocyte levels over 20% on hospitalization or which subsequently increased to over 20% following treatment had positive outcomes, but below 5% were deemed critically ill with corresponding high mortality [47]. Lymphocyte subsets in other studies further showed a decreased absolute T cell, CD4 T cell, cytotoxic (CD8+) T cell, and natural killer (NK) cell count, but with a lower normal range value for B cells [31]. T cell counts decreased significantly in COVID-19 cases of non-severe and severe patients, with severe patients having drastically reduced levels [31][48]. Song et al. reported an overall decreased lymphocyte subset including CD3+ T Cells, CD4+ T Cells, CD8+ T cells, and NK cells but with no significant difference between mild and severe patients, except for B cells, which were increased in severe patients [35].

Severe patients also had neutrophilia alongside lymphopenia, creating higher values in the neutrophil-to-lymphocyte ratio (NLR), which serves as a potential biomarker for increased systemic inflammation [31]. Increased NLR was associated with lung inflammation and the eventual development of critical patients with ARDS leading to an ultimately poor prognosis, and is another prospective marker for differentiating COVID-19 patients by severity [49][50]. Values above 3.3 of NLR for patients over 50 years of age showed a predictive deteriorative change from mild to severe disease at an average of approximately six days [50].

Cytotoxic T cells and natural killer cells are essential for an effective antiviral immune response. They were shown to be functionally exhausted in severe patients by the increased expression of NKG2A on lymphocytes, an inhibitory immune receptor on the cell surface which decreases its activity and may be correlated with disease progression [51]. NKG2A was shown to be upregulated in severe COVID-19 patients by Zheng et al., alongside decreased functional activity indicated from the decrease of intracellular cytokines CD107a, Membrane protein CD107a is correlated with NK cell activity and further cytokine secretion, with decreased function suggesting potential excessive lung inflammation is not due to overactivation of NK cells [52].

Further analysis by Demaria et al. confirmed lymphopenia and increased NKG2A expression in severe COVID-19 patients with pneumonia and ARDS, but also found a decrease in mature NK cells in patients with ARDS in both the peripheral blood and the bronchoalveolar fluid (BALF), indicating systemic deficiency instead of cell migration [53]. CD39 for a potential immunotherapy avenue of treatment, and found all to have been upregulated in the BALF of ARDS patients with a higher degree of overall expression than seen in the periphery [53]. Subsequent treatment in blocking NKG2A activation with the use of the monoclonal antibody monalizumab restored NK cytotoxic function, and could potentially recover NK antiviral activity in patients [53].

Patients with respiratory failure from severe SARS-CoV-2 commonly display one of two major forms of SARS-CoV-2 immune dysregulation: the “cytokine storm” phenotype, or more commonly, one characterized by targeted immunosuppression. Patients with the immunosuppression phenotype have elevated levels of IL-6 and IL-8, relatively lower levels of cytokines in other pathways, and the virtual absence of a type I or type II IFN response [54]. One possible cause for this immunosuppression is excessive glucocorticoid levels, which may cause systemic inflammation, which is known to suppress HLA-DR expression on monocytes [55]. The elevated levels of IL-6 can increase cortisol levels through various mechanisms, including direct stimulation of the adrenal cortex and through induction of corticotropin-releasing hormone and adrenocorticotropin [54].

4. Co-Morbid Conditions and Genetic Risks Stoke Immunopathology of SARS-CoV-2

Pre-existing health risks demonstrate poorer clinical outcomes from SARS-CoV-2 [15][16]. and others, the incidence and morbidity associated with SARS-CoV-2 was highest among individuals with underlying chronic conditions including obesity, cardiovascular, hypertension, kidney, type 2 diabetes mellitus, and respiratory-related disease [56][57][58][59][60]. ACE2, which plays a critical role in the regulation of both underlying disease and SARS-CoV-2 entry, is essential for metabolic control of respiratory, vascular, myocardial, kidney, and pancreatic functioning, among others [61][62][63]. For example, in the case of metabolic disease, an upregulation of ACE2 that interacts with the Angiotensin-II type 1 receptor (AT1R) has pathologic pro-inflammatory and pro-fibrotic effects

ACE2 regulates angiotensin II, of which high levels can cause increased vascular permeability and lead to lung, cardiac, and vascular damage. As SARS-CoV-2 progresses, it activates immune cells, platelets, and coagulation factors, which can cause multiple organ failure and death. In a phase II trial, patients who received recombinant ACE2 saw a reduction in angiotensin II levels, which appeared to improve lung injury [14][64][65]. Recently, the process of inflammaging has received much attention which could explain some of the pathology that is seen in elderly patients with SARS-CoV-2 infection as the lungs of elderly individuals are characterized by chronic low-grade inflammation [66].

There have also been instances of acute cardiac inflammation and injury in convalescent COVID-19 patients. Regardless of preexisting conditions and infection severity, 78% of patients in a prospective cohort study who had recovered from COVID-19 showed some degree of cardiac involvement on cardiac magnetic resonance imaging [67]. The most common of which being myocardial inflammation, followed by regional myocardial scar and pericardial enhancement [67]. Severe pediatric COVID-19 patients without respiratory failure or comorbidity in Paris were reported to have myocarditis, diffuse inflammation, and an atypical Kawasaki disease, further indicating that SARS-CoV-2 or its induced systemic inflammation may have considerable effect on the cardiovascular system [68].

Other factors may include trained immunity, fewer comorbid risk factors, and the fact that children's lungs are still developing. Trained immunity is functional reprogramming of cells of the innate immune system to a more active state after stimulation by certain antigens, such as those from vaccinations or viral infections. These changes can affect local cells, such as lung macrophages and dendritic cells, as well as progenitor cells of monocyte and myeloid cell lines. It also activates NK cells and interferons, leading to strong innate immune responses that may help contain early infections and clear them more rapidly.

Children also less commonly have risk factors such as obesity, smoking, and comorbidities such as hypertension and diabetes mellitus. However, children who have these pre-existing factors or illnesses may still fall into high-risk categories and need appropriate monitoring. Additionally, since children's lungs are still developing, the alveolar epithelium have a greater capacity to regenerate, which may accelerate recovery (31). In contrast, adult patients have weaker adaptive immunity and in many SARS-CoV-2 cases, dysfunctional hyperactive innate immune responses in severe infections that is not commonly observed in children [69].

The majority of SARS-CoV-2 cases are among non-Hispanic whites, but racial and ethnic minorities are disproportionately represented. Ethnic minorities especially African American (AA) populations may have a greater risk of SARS-CoV-2 infections due to comorbidities like hypertension, cardiovascular disease, diabetes, chronic obstructive pulmonary disease (COPD), and asthma [70][71][72]. In addition, it was observed that AAs and Hispanics/Latinos when compared with non-Hispanic Whites had higher mortality associated with COVID-19 [72]. Additionally, they are more commonly subjected to crowded living conditions and reliance on public transportation.

Male patients generally have greater inflammation indices, more impaired liver and kidney function, and more complications than women do. They also generally have more significant lymphopenia and thrombocytopenia [73]. Evidence suggests that more men die than women, which may be due to sex-based immunological differences [74][75], including genetic differences in chromosome complement and different levels of sex hormones [76]. It is possible that administration of these hormones, such as via oral contraceptive, could keep estrogen levels high and therefore play a protective role [10].

5. Conclusions

Although we now have a few SARS-CoV-2 vaccines that have been approved by the FDA via EUA, a range of other immune interventions that are being explored, as a means to boost protective innate immunity and reduce damaging inflammatory responses, would be crucial in the fight against COVID-19. These immunomodulatory approaches could be utilized in combination with the current standard of care, the antiviral remdesivir and corticosteroid dexamethasone. Despite the challenges posed by this novel and rapidly spreading viral infection, the response from the scientific community has been tremendous with the development of several vaccine candidates and treatment options within a short duration of time, which will serve as a template for future responses to pandemics.

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