Severe acute respiratory syndrome Coronavirus-2 infection: A synopsis of the host immune responses and viral immune evasion strategies involved

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Abstract

The novel coronavirus designated as SARS-CoV-2 is the etiological agent of coronavirus disease 2019 (COVID-19), which rendered the care of the global health powerless and plunged the world economy into a historic decline. This disease is characterized by different clinical pictures; ranging from asymptomatic mild phase to severe illness with acute respiratory distress syndrome (ARDS), in addition to having no specific therapy. The protective immunity involving solid CD4+ T-cells, viral specific CD8+ T-cells and the neutralizing immunoglobulins have been established in most of the convalescent COVID-19 individuals. On the other hand, the host immune response to severe COVID-19 infection has been attributed to the inflammatory cytokine storm, and to influx of the activated immune cells to the lungs; leading to severe pneumonia, extensive ARDS and finally to death. Despite of this, the protective and pathogenic aspects of the human immunity have not been fully elucidated. Recent attempts conducted by several published research works have focused on information derived from the immune responses to the severe acute respiratory syndrome-related coronavirus diseases (mainly; SARS and MERS). However, these works lack sufficiency due to variations in the transmissibility, virulence, host-virus interactions and the immune evasion mechanisms. Hence, adequate understanding of the host immune response mechanisms to SARS-CoV-2 will generate the impetus towards effective control and preventive measures. The objectives of this article were to provide an overview of the host immune responses to SARS-CoV-2 infection, the viral immune evasion strategies, and to define certain knowledge gaps that require further studies.

Keywords: SARS-CoV-2, COVID-19, T-cells, Immune response, Immune evasion
1. Introduction

Coronaviruses are spherical-shaped enveloped, non-segmented positive-sensed RNA viruses, which belong to the subfamily Coronavirinae of the family Coronaviridae. According to Su et al., (2016); Chan et al., (2020); Chen et al., (2020a), this large family of human, veterinary and zoonotic viruses comprises four different genera mainly: Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. The seven coronaviruses documented to infect humans have been grouped into two main categories on the basis of their pathogenicity. Low pathogenic human coronaviruses (HCoV), which include HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1 viruses that cause mild (common cold-like) respiratory illness, as reported by Pyrc et al., (2006); Van Der Hoek, (2007); Shurin et al., (2020). The second category are the highly pathogenic HCoV viruses, particularly; Severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Recent studies conducted by Cleri et al., (2010); Nacem, (2014); Rokni et al., (2020); Yang et al., (2020a) reported that these viruses are responsible for the major epidemics in the past two decades. Infections with the latter group have been reported to cause severe immunopathological responses, which result in fatal pneumonia.

The novel SARS-CoV-2 that causes the dreaded pandemic coronavirus disease 2019 (COVID-19), is the most contagious of these viruses. As of February 9, 2021, the virus was detected in over 105.4 million confirmed cases, with more than 2.3 million deaths globally, while several nations are still battling with the second wave of the disease (WHO, 2021). Recently, Orakpoghenor et al., (2020) revealed that clinical presentations of COVID-19 range from the most predominant asymptomatic or mild stage to severe respiratory illness. According to Inandikhoglu and Akkoc, (2020); Mortaz et al., (2020), the majority of patients which progressed to the severe stage exhibited immunological dysregulations, associated with inflammatory cytokine storm (ICS) and lymphopaenia. Most potential therapies currently under evaluations have focused on direct elimination of the virus and/or vaccines development, while ignoring the role of the host immune response (Liang et al., 2020).

A recent work conducted by Sariol and Perlman, (2020) highlighted that although the protective and pathogenic immune responses in COVID-19 patients have been speculated; the host immune response and viral evasion strategies have not been fully elucidated due to novelty of the virus. The protective solid immunity involving CD4+ T-cells, SARS-CoV-2 specific CD8+ T-cell responses (Grifoni et al., 2020), and positive antibody responses (Bao et al., 2020) have been described in convalescent COVID-19 patients with normal disease course and no hospitalization. On the other hand, Bonam et al., (2020); Prete et al., (2020) reported that the insufficient and detrimental immune responses characterized by ICS, and the influx of activated immune cells to the lungs with eventual development of acute respiratory distress syndrome (ARDS); were observed in severe COVID-19 individuals requiring positive pressure oxygen therapy, and often intensive care hospitalization.

According to Wu and McGoogan, (2020), the pro-inflammatory cytokines-driven ARDS is the most critical stage of SARS-CoV-2 infection that can result in multi-organ failure and death. Liang et al., (2020) reported that limited understanding of the immune responses caused by SARS-CoV-2 makes it difficult for clinicians to avert patients from complications of ARDS and pulmonary fibrosis. Therefore, it is imperative to regulate the aberrant host immune responses when managing severe SARS-CoV-2
infected patients. However, achieving this important task seems to be challenging; hence, there is a need for adequate knowledge of the host immune responses to SARS-CoV-2.

Liang et al., (2020); Shah et al., (2020) reported that although significant efforts have been made to unravel the immunity surrounding this pandemic; however, much of these efforts were predictive knowledge derived from the host immune responses to acute respiratory syndrome-related coronavirus diseases, particularly severe acute respiratory syndrome (SARS) and Middle-East respiratory syndrome (MERS). Recent studies of Sariol and Perlman, (2020); Shurin et al., (2020); Yang et al., (2020b) highlighted that no doubt, this would provide valuable hints toward the fight against COVID-19, owing to the fact that these related viruses share about 80 % of sequence identity; use the same entry receptor and cause similar acute respiratory syndromes. However, the information obtained might not accurately depict the novel COVID-19 dynamics, because of the differences in several epidemiological and biological characteristics including; type of host cells mostly infected (Liang et al., 2020); virulence, host-virus interactions, immune escape pathways (Shurin et al., 2020), and transmissibility among these related viruses (Yang et al., 2020b; Zhang et al., 2020a).

Furthermore, central to the development and identification of excellent vaccine candidates and fine-tuning of COVID-19 control measures depend on good understanding of immunity to the SARS-CoV-2. This has become critical now, as some promising COVID-19 vaccines, notably, Moderna mRNA-1273, Pfizer/BioNTech BNT162b2, Gamaleya Sputnik V, and Sinopharm BBIBP-CorV, have reached the advanced stage 3 clinical trials, and are gaining approval for administration from several countries (https://covid19.trackvaccines.org/vaccines/). In addition, excellent knowledge of immunity to SARS-CoV-2 infection might improve the measures for using immune therapy as an adjunct to stop patients from developing ARDS, and helps in combating the pandemic. Therefore, this review summarizes the host immune responses to SARS-CoV-2 infection, and how the virus evades such responses. It also highlights some gray areas of research requiring further exploration.

2. Host immune responses in COVID-19

Infection with SARS-CoV-2 triggers serious immunological responses from both host innate and adaptive immune systems. Several studies conducted by Liang et al., (2020); Shah et al., (2020) revealed that these complex responses involve recognition of the whole SARS-CoV-2 or its components by pathogen recognition receptors (PRRs); recognition of viral spike (S) and nucleocapsid (N) proteins by the B cells, as well as presentation of the viral antigens by major histocompatibility complexes (MHC) to T cells. These responses lead to type I interferon (IFN) response; increased cytokine secretion, antibody production and cytolytic effects; with the aim of eliminating the invading SARS-CoV-2. Moreover, Shi et al., (2020); Shurin et al., (2020); Thevarajan et al., (2020) added that the host immune responses in COVID-19 seem to be in two-stages; a protective response observed in most patients with mild or no clinical symptoms, and pathogenic response characterized by hyper-activation of some subsets of immune cells; increased viral propagation, ICS, ARDS and massive destruction of the affected tissues, which are observed in severe COVID-19 patients when the protective response is impaired.

2.1. Innate immune responses

A recent work conducted by Vabret et al., (2020) highlighted that an effective innate immune response that involves pro-inflammatory cytokines; IFN type I response and its downstream cascades, which culminates in controlling viral replication and induction of effective adaptive immune response, constitutes the primary line of defense against invading viruses. Shah et al., (2020) added that interferons secreted by most innate immune cells are not only efficient in impeding cell proliferation, but
equally modulate apoptosis, immune response and act as secondary immune messengers to stimulate the other body cells.

In COVID-19, PRRs present on many immune cells; particularly Toll-like receptors (TLR) 3, 7, and 8, are known to be the earliest host factors to identify SARS-CoV-2 surface epitopes (Shah et al., 2020). Meanwhile, as with SARS and MERS, the pathogen-associated molecular patterns (PAMPs) represented by the viral RNA are recognized by the intracellular sensors such as RIG-I; leading to downstream signaling cascades that eventually activate NF-κB, and IRF3 transcriptional activities. As reported by Prompetchara et al., (2020), this results in enhanced IFN production and expression of pro-inflammatory cytokines. Lokugamage et al., (2020) demonstrated that SARS-CoV-2 is sensitive to IFN pretreatment. Likewise, Cai et al., (2020); Chu et al., (2020) revealed that increased concentration of types I and II pneumocytes; alveolar macrophages, plasma cells and foam cells, were consistently reported in SARS-CoV-2 infected patients.

A previous work of Tanaka et al., (2016) revealed that in an attempt to clear viral particles and control pulmonary inflammation, cytokines were employed; however, rapid and massive release of cytokines could cause deleterious effects in the host. According to Wan et al., (2020); Zhou et al., (2020). Interleukin (IL)-6, which produces CD14+CD16+ inflammatory monocytes, is identified as the key inflammatory cytokine that mediates the frequently reported cytokine release syndrome associated with COVID-19. Recently, Huang et al., (2020); Mehta et al., (2020); Yang et al., (2020c) proposed that a cytokine profile comparable to patients with secondary hemophagocytic lymphohistiocytosis is well documented in severe COVID-19; depicting cytokine storm, due to excessive immune activity. This includes increased levels of IP-10; MCP-3, MCP1, HGF, MIG, MIP-1α, GCSF, TNF-α, MCF1 (CCL2), IL-2 and IL-7. Furthermore, Huang et al., (2020); Shurin et al., (2020) reported that these cytokines may help in grading the prognosis of each patient; as dissimilar expression profiles are observed in patients with different COVID-19 severity. For instance, the levels of IP-10; MCP-3, MCP1, HGF, MIG, MIP-1α, GCSF and TNF-α, are reported to be significantly higher in critical patients, compared to their expression in moderate disease. On the other hand, IP-10 and MCP-3 were found to be outstanding predictors for the progression of COVID-19 infection.

Notwithstanding, there is general paucity of data on innate immune responses to SARS-CoV-2, other than the elevated levels of acute-phase reactants and ICS. Most of the recent reports focused on severe outcomes and adaptive immune responses (Azkur et al., 2020). Therefore, more intensive studies are required to elucidate these important components of the immune response to COVID-19.

2.2. Adaptive immune responses

In an effort to eliminate the invading SARS-CoV-2 and preclude disease progression to severe stages, the host may employ specific adaptive immune responses. These involve combined induction of humoral and virus-specific T lymphocytes, to provide optimal protective immunity.

2.2.1. Humoral immunity

Virus neutralization is crucial to impede the spread of the invading virus throughout the body tissues. Recent studies conducted by Bao et al., (2020); To et al., (2020); Wu et al., (2020), reported that positive humoral immune response that is characterized by high titer of neutralization antibodies such as; IgM and IgG targeting the viral S and N proteins, are found within the sera of most SARS-CoV-2 exposed individuals. Induction of the IgM is earlier and transient, while IgG possess longer half-life and lower molecular weight, hence provide longer protection with efficient tissue penetration. Similarly, the minority of patients particularly those with either asymptomatic or severe infections mount little detectable antibodies. In fact, potential full recovery in the absence of antibodies has been reported in some cases, as highlighted by Altmann, (2020).
As reported by Zhao et al., (2020), the seroconversion rates of IgM, and IgG observed in COVID-19 patients were documented to be 82.7 % and 64.7 %; respectively, whereas the median seroconversion times were evaluated to be around 12th and 14th days post onset of symptoms, respectively. Thus, most patients become seropositive to the virus and negative for SARS-CoV-2 PCR within 28 days (Gorse et al., 2020). For how long these antibodies will remain in recovered patients has not been fully delineated (Liang et al., 2020). However, recently Long et al., (2020); Seow et al., (2020) revealed that for the naturally acquired SARS-CoV-2, the antibodies begin to disappear 2-3 months post infection. Although, Stephens and McElrath, (2020) reported that antibody titers always decrease after an acute phase of infection. Accordingly, in convalescent COVID-19 patients, the decline in IgG neutralizing antibodies to SARS-CoV-2, may fuel the trepidation about susceptibility to reinfection.

Altmann, (2020) highlighted that SARS-CoV-2 spike antigen-binding responses correlate well with the functional virus neutralization. Conversely, some studies conducted by Jiang et al., (2020); Tan et al., (2020a) on antibody responses in COVID-19; have associated higher IgG and IgM titer against viral S and N proteins at different stages of the disease with older age; worse clinical readouts and highly unfavorable prognosis. Accordingly, Iwasaki and Yang, (2020); Tetro, (2020) suggested potentially detrimental effects of the antibodies in some COVID-19 patients in a possible antibody-dependent enhancement (ADE) phenomenon. Therefore, careful and more elaborate researches on subclasses of IgG, IgM and IgA; recognizing at least SARS-CoV-2 specific S or N proteins would unravel the applicability of ADE in COVID-19, provide answers to several unknowns regarding the development and stability of humoral immune response in COVID-19, and might also support the development of fast, reliable and non-expensive alternative means for early diagnosis of SARS-CoV-2 infection (Shurin et al., 2020). Moreover, beneficial insights gained from studying the subclasses of these immunoglobulins, which correlate with recovery as opposed to worsening of COVID-19 infection, will inform us the type of antibodies that has to be assessed when selecting the best possible SARS-CoV-2 vaccine.

2.2.2. Cell-mediated immunity

As proposed by Grifoni et al., (2020), a robust of T-cell antiviral immune response comprising solid CD4+ T cell response that helps in antibody production, and viral specific CD8+ T cells that eliminate virus-infected cells, have been established in average COVID-19 recovered patients; who had a normal disease course with no recourse to hospitalization. The activation of T-cells by N and S proteins of SARS-CoV-2 is documented to occur within the first week of infection, whereas the virus-specific memory CD4+ and CD8+ T-cells increase about 2 weeks post activation. These reportedly remain detectable although at lower levels for at least 100 days. Therefore, the observed long-lived T-cell responses might dispel the lay press belief about failure of the host immune system to mount protective and lasting response to SARS-CoV-2 (Stephens and McElrath, 2020).

Active immune response against many viral infections hinges on activation of cytotoxic T lymphocytes to eliminate the virus-infected cells. According to the recent study of Shurin et al., (2020), massive tissue damage associated with ICS and hyper-activation of virus-specific CD8+ cells during COVID-19 infection, may dysregulate the peripheral tolerance machinery and allows the development of autoimmune pathology after patient recovery. Moreover, Diao et al., (2020); Zeng et al., (2020) added that a dramatic cytokine release drive depletion, and exhaustion of total CD4+ and CD8+ T cells is often reported in acute phases of SARS-CoV-2 infection; as patients progressed from prodromal to overtly symptomatic stages. This significant reduction in T cells levels exposes COVID-19 patients to secondary infections; prolonged virus clearance and reduced survival rate, as proposed by Zheng et al., (2020). Therefore, intensive
research on subpopulations of T lymphocytes; for their vulnerability and roles in COVID-19 progression and recovery will be necessary. Furthermore, Shurin et al., (2020) highlighted that very limited information regarding SARS-CoV-2 proteins-specific T cells subsets in COVID-19 patients is known; hence, comprehensive analysis of these cells especially after recovery is needed, to predict and minimize outcomes of immune dysregulation during infection.

Altmann, (2020); LeBert et al., (2020) reported that T-cells from SARS and COVID-19 convalescent patients have been documented to share similar antigen responsiveness to conserved regions of nucleocapsid protein. In addition, exposure to the circulating common cold coronaviruses provides some level of pre-existing immunity to the novel SARS-CoV-2. This has been evidenced through the significant cross-reactive T cells responses in blood samples of people who had never been exposed to the SARS-CoV-2, but have experienced at least three of the four common cold coronavirus infections during their life. However, it is still not clear, whether the observed cross-reactivity provides any kind of protective immunity to COVID-19 (Grifoni et al., 2020).

3. SARS-CoV-2 immune evasion strategies

Recent studies conducted by Shah et al., (2020); Sariol and Perlman, (2020) revealed that one of the most effective antiviral machineries employed by the immune cells is the secretion of interferons (IFN). An early type I IFN response plays important role in protection against severe diseases, and prevention of aberrant pro-inflammatory cytokine release. However, coronaviruses have developed various immune evasion mechanisms, to prevent detection by PRRs and inhibit IFN-I induction and signaling pathways leading thus to enhanced pathogenesis.

As a member of Betacoronavirus group, SARS-CoV-2 is conceived to develop immune evasion mechanisms similar to those of SARS-CoV and MERS-CoV, which have been extensively reviewed and discussed by Kindler et al., (2016); Thornbrough et al., (2016); Kikkert, (2020). Briefly, these related coronaviruses suppress type I IFN response (Cameron et al., 2012; Comar et al., 2019); induce T cells apoptosis (Yang et al., 2005; Bahl et al., 2010), activate direct elimination of activated T Cells (Chu et al., 2015) and down regulate antigen presentation via MHC class I and II, leading thus to overall diminished T cells responses (Shokri et al., 2019). However, whether such SARS-CoV-2 has evolved these evasion strategies and/or ought for additional possible immune escape mechanisms like viral mutations, immune exhaustion and deviation, and biased Th2 type response remain to be elucidated.

The recent study of Singh et al., (2020) revealed that SARS-CoV-2 is able to stay undetected within host cells for longer time than many influenza viruses or other coronaviruses, thus efficiently evading the host immune detection at the early stages of infection. Moreover, the virus induces inadequate types I, II and III IFN signatures in SARS-CoV-2 infected cell lines; primary bronchial cells and a ferret model, as revealed by Blanco-Melo et al., (2020); Chu et al., (2020). Similarly, severe COVID-19 patients have been shown to possess impaired IFN responses; dysregulated cytokines and chemokines profiles; thus exacerbate inflammatory responses, owing to low levels of IFN production or signaling (Chen et al., 2020b; Hadijadi et al., 2020; Yang et al., 2020c). The low-level synthesis of type I and type III INFs with sufficient interferon-stimulated gene (ISG) expression, alongside with the elevated chemokines secretion during SARS-CoV-2 infection, result in the decreased antiviral genes transcription, which in turn drives the development of severe COVID-19 clinical features (Blanco-Melo et al., 2020; Shah et al., 2020). In addition to their effects on the host IFN pathway, SARS-CoV-2 viral proteins such as nonstructural proteins and open reading frames are reported to impede several other innate immune signaling proteins resulting in the progression of COVID-19 infection (Gordon et al., 2020).

Previous studies conducted by Brandstädter and Yang, (2011); Schuster et al., (2016) revealed that the
natural killer (NK) cells play critical role in the defense against viral infections. Their activation results in targeted killing of infected/activated cells; cytotoxic degranulation and release of cytokines, and helps to modulate the host adaptive immune responses. Reduction in the numbers and blunted functions of the NK cells such as CD56\textsuperscript{dim}CD16\textsuperscript{*} and CD56\textsuperscript{bright}CD16\textsuperscript{+/-} cells, have been reported from several COVID-19 studies (Market et al., 2020; van Eeden et al., 2020; Bao et al., 2021). According to Song et al., (2020); van Eeden et al., (2020); Zheng et al., (2020), abridged count of these important NK cells is associated with decreased clearance of infected/activated cells; diminished cytotoxicity, impaired production of chemokines, IFN-γ and TNF-α, and unchecked elevation of the tissue-damaging inflammation markers leading to severe COVID-19 features. However, while lungs NK cells do not express ACE2; the entry receptor for SARS-CoV-2 (Travaglini et al., 2020), the reduced NK cell counts and function have not been adequately linked to the direct effects of the virus. A recent study of Vabret et al., (2020) added that impaired maturation of the NK compartment; or migration of the circulating NK cells into the lungs or to the other peripheral tissues of COVID-19 patients, have been hypothesized to be the possible reasons behind their reduced counts.

Furthermore, severe lymphopaenia in the CD4\textsuperscript{+} T-cell, CD8\textsuperscript{*} T-cell and B-cell previously observed in some cases of SARS and MERS (Wong et al., 2003; Li et al., 2004), is another potent escape mechanism employed by SARS-CoV-2, to cause defects in the host antiviral and immune regulatory immunity, as reported by recent research works conducted by Azkur et al., (2020); Liu et al., (2020); Tan et al., (2020b); Wang et al., (2020a). Lymphopaenia in coronavirus infections is reported to occur via three main mechanisms mainly; impaired lymphopoiesis, redistribution of the circulating lymphocytes, and apoptosis or direct destruction of the lymphocytes (Rokni et al., 2020). The exact mechanism by which SARS-CoV-2 causes lymphopaenia has not been fully elucidated. However, it is speculated that the virus infects the T-lymphocytes through the receptor-dependent or the S protein-mediated membrane fusion thereby inducing the T-cell apoptosis and autophagic cell death of the peripheral blood mononuclear cells (Wang et al., 2020b; Xiong et al., 2020). Besides reduction in the circulating T cells, SARS-CoV-2 equally directs the increased expression of the inhibitory receptors such as PD-1, TIM-3 and TIGIT on its surface, leading to exhaustion and loss in functions of the effector T cells, in order to overcome the host antiviral immune response (Chiappelli et al., 2020; Qin et al., 2020).

Conversely, in addition to the influence of SARS-CoV-2, possible compounding elements of the environmental factors; genetics and age of the patient, co-morbidity of renal diseases, cancer and allergic conditions among others may modulate the severity of COVID-19. For instance, age-dependent factors such as differential expression of ACE2 are conceived to modulate the immune responses to SARS-CoV-2, because although COVID-19 adult patients mount more robust T cell response, higher serum neutralizing antibody titers and better antibody-dependent cellular phagocytosis, the children and youth infected with SARS-CoV-2 were established to develop milder disease and lower mortality rate (Bunyavanich et al., 2020; Mortaz et al., 2020; Pierce et al., 2020).

Conclusion
The COVID-19 pandemic caused by SARS-CoV-2 is a multifactorial pathophysiological process involving pro-inflammatory cytokines; chemokines, blood cells, activated immune cells and residential tissue cells. The majorities of COVID-19 patients have mild to moderate illness, and normally recovers within one week developing protective T-cells and antibody immunity. However, the immunological dysregulations associated with lymphopaenia; eosinopaenia, extensive pneumonia and lung tissue damage, followed by ICS, ARDS, disseminated intravascular coagulation and multi organ failure are seen in severe diseases. The virus induced pro-inflammatory cytokine directed ARDS that is
consistently linked with severity and fatal COVID-19 outcomes, is evident following over-activation of some of the immune cells including; T cells, NK cells, B cells and antigen presenting cells.

Although the body of most COVID-19 patients recognizes the viral components such as the S and N proteins to mount an immune response leading to successful elimination of SARS-CoV-2; however, the virus has so far evolved several mechanisms especially in severe diseases to escape these immune responses. Notwithstanding, the majority of these evasion strategies have not been systematically delineated partly due to novelty of the virus. Thus, in spite of the growing immunological data about immunity to SARS-CoV-2 infection, there remain pressing unknowns, which necessitate further studies.

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Ethical approval

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