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Review Article

Orchestration of Host Immunity with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

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Abstract

The running COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) greatly sought the attention worldwide because of its high morbidity and mortality effects. The critical issues concerning the host immunological response against this virus as well as the evasive strategies of the host immunity by the virus is of major significance to understand the severity of the viral pathogenesis and infectivity. Current review thus focused on the host immunology in connection with the infectious SARS-CoV-2; and categorically discussed the innate immunity and adaptive immune mechanisms exerted by hosts against the viral attack.

Keywords: *COVID-19 Pandemic; Acute Respiratory Syndrome Coronavirus (SARS-CoV-2); Host Immunity; Viral Pathogenesis*

Introduction

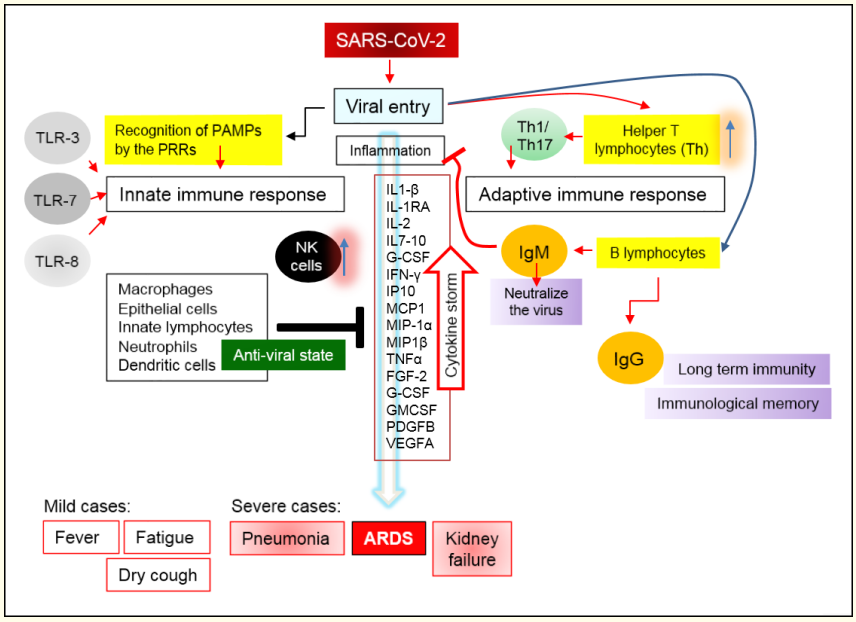
The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) starting from the December last in 2019, has so far accounted for nearly 418294 deaths with 7410510 million infected cases with the major clinical onset of the acute respiratory distress syndrome (ARDS) [1-3]. Bats, pangolins, snakes have been reported as the intermediate hosts facilitating the spill-over of SARS-CoV-2 from bats to the human [2,3]. The transmission mode of SARS-CoV-2 is then mainly attributed by human-to-human transmission via the respiratory droplets; and broadly the transmission rate elevated also due to the worldwide traveling of humans [3-8].

Genomic studies revealed that the virus consists of 14 open reading frames (ORFs): the first two ORFs at 5' UTR encoding the polyprotein (pp1a/ab, required for the viral replication) and 16 non-structural proteins (required for the transcription and replication), followed by the structural proteins; and at the 3' terminus, there remain the accessory genes with the flanking ORFs [11-13]. The major virulence factor of the SARS-CoV-2 has been pointed towards its spike (S) protein (encoded within the genes *orf8* and *orf3b)* which facilitates the viral entry into the host cells directly through the host surface receptor binding site (RBD) [3,10]. Human angiotensin-converting enzyme 2 (ACE 2, a metallopeptidase) which is known as the key molecule in the renin-angiotensin system acts as the cell entry receptor [12,13]. The antibody-dependent enhancement (ADE) of viral entry is also known [14]. The ADE mediated viral entry may take place whereby a neutralizing monoclonal antibody specifically targets the RBD of the spike, causing its conformational changes and the proteolytic activation that is necessary for the viral release into the host [4,10,14].

The evolution of the virus may occur due to the successive mutations and recombination processes which in turn result in the corresponding mutations at every replication cycle of the virus [6,7,11,15]. The pathophysiological impact has been well understood from various reports pondering the cytokine storm in the SARS-COV-2 infected patients [5,9]. This is to be mentioned that the Orf3b protein (product of the *orf3b* gene) may play a significant role in the viral pathogenesis [11]. Lots of reports on the evolution, mode of transmission, epidemiology, the escaping strategies of the host immunity along with the concomitant pathogenesis, diagnosis, the possible preventive care with the anti-viral therapy and the vaccination strategies have been published so far. Most importantly, recent reports showed that during the viral infection, the uncontrolled immune response triggered by the hyperactivation of macrophages and monocytes results in an increase in the neutrophils, IL-6 and the C reactive proteins with a concomitant decrease in the total number of lymphocytes [16]. Present review further outlined the immunological cascades towards the infective virus in order specifically point to the roles of the host immune cells upon SARS-CoV-2 infection.

Host immune response upon viral entry

An arranged system of the cellular innate immunity usually recognizes the virus after the entry along the respiratory tract, and then a downstream signaling response by the protective immune cells (alveolar macrophages, airway epithelial cells, the innate lymphocytes, neutrophils and the dendritic cells) takes place to launch the anti-viral state [3,4]. As shown in figure 1, such innate immune response signaling cascade is triggered by the recognition of pathogen-associated molecular patterns (PAMPs) by the pattern recognition receptors (PRRs); and the toll-like receptors (TLRs) 3, TLR-7 and TLR-8 are expressed [3]. Besides, the adaptive immune responses (1) by the virus-specific T cells (to impart the cell-mediated immunity whereby Th1/Th17 by the Helper T lymphocytes can contribute to lower the inflammatory response), and (2) by the B-lymphocytes (to impart the humoral immunity whereby the B lymphocytes mediate the production of specific immunoglobulins especially IgM to neutralize the virus) are also activated [16]. This is to be noted that the detection of IgG in the SARS-CoV-2 infected patients is suggestive of the long term exposure towards the virus (associated with the long-term immunity and immunological memory), and that the detection of IgM in the serum is suggestive of a recent exposure to the virus [16]. A study using blood samples from a 47-year-old SARS-CoV infected patient showed that the titers of IgM and IgG progressively increased from day 7 to day 20 [16,20]. Besides, it was noticed that around 7 - 9 days after the onset of the SARS-CoV-2 typical symptoms, the concentrations of the T helper cells (Th), Natural Killer cells (NK) and B cells increased in the blood sample [20].



Figures 1: *SARS CoV 2 and host immunity. The innate immune response is triggered by the recognition of pathogen-associated molecular patterns (PAMPs) by the pattern recognition receptors (PRRs); and the toll-like receptors (TLRs) 3, TLR-7 and TLR-8 are expressed. The adaptive immune responses are mediated by the virus-specific T cells and B-lymphocytes. The concentrations of the T helper cells (Th), Natural Killer cells (NK) and B cells are increased in the infected individuals. Besides, the elevated levels of pro-inflammatory cytokines are noticed (i.e., the cytokine storm): interleukin 1-β (IL1-β), the interleukin-1 receptor antagonist (IL-1RA), IL-2, IL7 to IL-10, granulocyte colony stimulating factor (G-CSF), interferon-γ (IFN-γ) inducer protein (IP10), monocyte chemotactic protein-1 (MCP1), the macrophage inflammatory protein-1α (MIP-1α), MIP1β, tumor necrosis factor (TNFα), basic fibroblast growth factor-2 (FGF-2), granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GMCSF), platelet derived growth factor (PDGFB), and vascular endothelial growth factor A (VEGFA), which in turn cause the onset of the acute respiratory distress syndrome (ARDS), respiratory failure, organ failure leading to death.*

Therefore, considering the deadly impact of the COVID-19 pandemic, it is of the highest priority to study the human immune responses during the SARS-CoV-2 infection and pathogenesis together with (1) the associated functions of the virus-specific T cells and the B-lymphocytes; and (2) on the production of immunoglobulins IgG and IgM (Figure 1) which in turn may allow the rapid identification of the SARS-CoV-2 infection [16]. In course of immunopathological facets, although it is said that nearly 80% of the infected individuals experience mild or null symptoms (fever, fatigue and dry cough); however, in severe cases the SARS-CoV-2 infected patients have been reported to experience lymphopenia and interstitial pneumonia with the elevated levels of pro-inflammatory cytokines (Figure 1): interleukin 1-β (IL1-β), the interleukin-1 receptor antagonist (IL-1RA), IL-2, IL7 to IL-10, granulocyte colony stimulating factor (G-CSF), interferon-γ (IFN-γ) inducer protein (IP10), monocyte chemotactic protein-1 (MCP1), the macrophage inflammatory protein-1α (MIP-1α), MIP1β, tumor necrosis factor (TNFα), basic fibroblast growth factor-2 (FGF-2), granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GMCSF), platelet derived growth factor (PDGFB), and vascular endothelial growth factor A (VEGFA) [16-19]. The massive release of such cytokines generate the so-called "cytokine storm", inducing the ARDS, respiratory failure, organ failure followed by death [16].

Major escaping strategies of the host immunity and the viral pathogenesis

The pathogenesis of the virus is vivid through its movement along the bronchial tubes to the lungs, causing the mucous membrane of the lungs inflamed and hard resulting in the shortness of breath and the ARDS [3,4,6]. Cells of the innate defense machineries including the alveolar macrophages, the lymphoid cells and the dendritic cells are concomitantly avoided by the virus [4]. As mentioned earlier, the elevated levels of the inflammatory chemokines and cytokines result in the ultimate acute lung injury [11].

As stated earlier, the spike protein binds to the ACE 2 receptor of the human host and after such receptor engagement, the cellular surface serine protease TMPRSS2 (a plasma membrane-associated type II transmembrane serine protease) is also used by the virus to trigger the spike protein to facilitate the membrane fusion that is necessary for the release of the viral contents into the host cell cytosol [8,9,11]. After the attachment of the virus by the interaction between the S1 region of the S protein at the RBD site and its receptor [10,21], the virus enters the host cell cytosol by the cathepsin mediated proteolysis of the S protein with the subsequent fusion of the viral and cellular membranes within the acidified endosomes [10]. The translation of the replicase gene starts eventually.

As reported earlier, the viral RNAs avoids recognition by the innate immune RNA sensors by adding a cap-structure to its 5′-end [4]. Moreover, during the transcription, the viral nucleoprotein may impart a unique ability to steal the mRNA cap-structures; i.e. the short, 5′-capped transcripts produced by the cellular DNA dependent RNA polymerase II from the host mRNAs; the so called "cap-snatching" mechanism, facilitating the viral mRNA transcription [4,16,22]. The viral endoribonuclease activity further helps in the avoidance of the protein kinase R (PKR) and the 2'-5' Oligoadenylate Synthetase (OAS)/RNAse L system which is one of the IFN effector pathways machineries [23].

Conclusion

The SARS-CoV-2 pathogenesis mainly depends on the viral escaping potential of the host innate immunity. The present review schematically outlined the host immune response in terms of both innate and adaptive immunity against the SARS-CoV-2 viral infection as well as emphasized on viral pathogenesis based on the elevation of the pro-inflammatory cytokines as well as the viral potential to escape the host immunity. The information drawn here are apparently not new; nevertheless, the categorical presentation of the host immune system activation by the viral entry may further increment the existing knowledge on the SARS-CoV-2 pathogenesis.

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Conflict of Interest

Authors have declared that they have no conflict of interest.

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Bibliography

1. WHO (World Health Organization) Coronavirus diseases (COVID-19) Dashboard (2020).
2. Huang C., *et al.* "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *Lancet.* 395.10223 (2020): 497-506.
3. Maniha SM., *et al.* "Ongoing COVID-19 Pandemics by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the Host Protective Immunity Response: A Simple Outline". *EC Emergency Medicine and Critical Care* 4.6 (2020): 103-108.
4. Kikkert M. "Innate Immune Evasion by Human Respiratory RNA Viruses". *The Journal of Innate Immunity* 12.1 (2020): 4-20.
5. Ralph R., *et al.* "2019-nCoV (Wuhan virus), a novel Coronavirus: human-to-human transmission, travel-related cases, and vaccine readiness". *Journal of Infection in Developing Countries* 14 (2020): 3-17.
6. Cascella M., *et al.* "Evaluation and Treatment Coronavirus (COVID-19)". *Stat Pearls* (2020).
7. Lu R., *et al.* "Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding". *Lancet* 395.10224 (2020): 565-574.
8. Lai CC., *et al.* "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges". *The International Journal of Antimicrobial Agents* 55.3 (2020): 105924.
9. Lu R., *et al.* "Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding". *Lancet* 395.10224 (2020): 565-574.
10. Fehr AR and Perlman S. "Coronaviruses: an overview of their replication and pathogenesis". *Methods in Molecular Biology* 1282 (2015): 1-23.
11. Abduljalil JM and Abduljalil BM. "Epidemiology, genome, and clinical features of the pandemic SARS-CoV-2: a recent view". *New Microbes and New Infections* 35 (2020): 100672.
12. Chu H., *et al.* "Comparative tropism, replication kinetics, and cell damage profiling of SARS-CoV-2 and SARS-CoV with implications for clinical manifestations, transmissibility, and laboratory studies of COVID-19: an observational study". *The Lancet Microbe* 1.1 (2020): e14-e23.
13. Xia S., *et al.* "Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion". *Cell Research* 30 (2020): 343-355.
14. Wan Y., *et al.* "Molecular Mechanism for Antibody-Dependent Enhancement of Coronavirus Entry". *Journal of Virology* 94.5 (2020): e02015-e02019.
15. Su S., *et al.* "Epidemiology, genetic recombination, and pathogenesis of coronaviruses". *Trends in Microbiology* 24 (2016): 490-502.

16. Di Mauro Gabriella., *et al.* "SARS-Cov-2 infection: Response of human immune system and possible implications for the rapid test and treatment". *International Immunopharmacology* 84 (2020): 106519.

17. Zhang W., *et al.* "The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China". *Journal of Clinical Immunology* 214 (2020): 108393.

18. Coperchini F., *et al.* "The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system". *Cytokine and Growth Factor Reviews* (2020): 25-32.

19. Noor R. "Anti-viral drugs against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection triggering the COVID-19 pandemic". *Tzu Chi Medical Journal*.

20. Thevarajan I., *et al.* "Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19". *Nature Medicine* 26.4 (2020): 453-455.

21. Cheng PK., *et al.* "Viral shedding patterns of coronavirus in patients with probable severe acute respiratory syndrome". *Lancet* 363.9422 (2004):1699-700.

22. De Vlugt C., *et al.* "Insight into Influenza: A Virus Cap-Snatching". *Viruses* 10.11 (2018): 641.

23. Kindler E., *et al.* "Early endonuclease-mediated evasion of RNA sensing ensures efficient coronavirus replication". *PLOS Pathogens* 13.2 (2017): e1006195.

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