Review Article

DEADLY INFLAMMATORY CYTOKINE STORM AS IMMUNE RESPONSE IN COVID-19 PATIENTS

Muhammad Shahbaz Aslam[1], Muhammad Saeed Qureshi[2], Zunaira Kanwal[3], Tooba Hameed[4], Khawar Amin[5], Ayesha Ahmad[6]

ABSTRACT

Coronavirus disease 2019 (COVID-19) outbreak which is caused by infection with SARS-CoV-2 was declared as a massive threat to international health by WHO in March'2020. This SARS-CoV-2 infection leads to immune reactions in the host known as cytokine storm, dysregulation in the host immune system leading to uncontrolled release of cytokines. Several clinical studies emphasize pertinent changes occurring in both innate and adaptive immune systems of the human body in response to SARS-CoV-2. As the world must live amidst the current ongoing virus, understanding the immunology of the disease can assist in disease containment and the development of more effective vaccines and therapeutics to prevent and treat patients infected with COVID-19. Here, we have discussed the changes in the host immune response to infection by SARS-CoV-2, mechanism of cytokine storm & association of other major cytokines.

Key Words: SARS-CoV-2, COVID-19, Acute respiratory distress syndrome

doi: https://doi.org/10.51127/JAMDCV3I3RA01

How to cite this:
Aslam MS, Qureshi MS, Kanwal Z, Hameed T, Amin K, Ahmad A. Deadly inflammatory cytokine storm as immune response in COVID-19 patients. JAMDC. 2021; 3(3): 126-133
doi: https://doi.org/10.51127/JAMDCV3I3RA01

INTRODUCTION

Coronaviruses (CoV) are a class of viruses that specifically targets respiratory systems and belong to the coronaviridae family.[1] They have been reported to infect birds and mammals including humans and cause infections of the upper and lower respiratory tract and severe acute respiratory syndrome (SARS).[2] Based on genetic studies, coronaviruses have been categorized into three major groups' alpha, beta, and gamma-coronaviruses.[2] The primary host reservoir of alpha and beta-coronaviruses are reported to be bats and the analysis of alpha and beta-coronavirus genera was confirmed by their presence in wild mammals like bats, hedgehogs, rodents, and lagomorphs.[3] The SARS epidemic of the year 2003 witnessed 8096 cases in 25 countries and indicated the possible health threat by the transmission of Coronavirus (CoV) from bats to humans and by its ability to diversify through recombination rapidly.[4] Coronaviruses have also been reported to be the causative agents of some earlier respiratory linked outbreaks that include SARS-CoV and MERS-CoV. Later, in December 2019, an uncommon infectious disease spread among people from the wild animal and seafood market of Wuhan, China, with initial symptoms like pneumonia. A global emergency was declared immediately by the WHO due to the rapid transmission of this contagious disease as the number of cases reached an alarming stage with over 82,000 cases in 27 countries by February 2020.[5,6] By March 10, 2020, the disease further progressed to a pandemic with

[1]Assistant Professor Biochemistry, School of Biochemistry & Biotechnology, University of the Punjab, Lahore.
[2]Professor Biochemistry, Akhtar Saeed Medical & Dental College, Lahore.
[3]Associate Professor Biochemistry, Allama Iqbal Medical College, Lahore.
[4-6]Students Biochemistry, School of Biochemistry & Biotechnology, University of the Punjab, Lahore.

110,000 infectious cases and 4000 deaths globally.[7]

The disease caused by this novel coronavirus 2019 (SARS-CoV-2) was named COVID-19 by WHO in February 2020.[8,9] Among the coronavirus family, it is found to be the 7th severe disease-causing coronavirus that infects humans and is found to be the causative agent of COVID-19. The genomic studies of this virus show that SARS-CoV-2 is not intentionally manipulated and is not a lab-controlled virus instead it is a naturally occurring virus from the coronavirus family. SARS-CoV-2 shows 76.9 % genomic sequence similarity with SARS-CoV and is reported to be an enveloped RNA virus.[10]

The comparative study of SARS-CoV-2 with SARS and MERS coronavirus suggested its origin from beta coronavirus and also confirmed their structural similarity due to the presence of four common structural proteins (spike, nucleocapsid, membrane, envelope), other accessory proteins, and sixteen non-structural proteins as well. The spike protein (S) containing an S1 subunit and S2 subunit at N-terminal and C-terminal respectively aids receptor binding and membrane fusion of the virus with the cell. To get entry into the host cell, the (S) protein of SARS-CoV-2 requires an appropriate binding with the ACE2 receptor of the host. It has also been reported that the receptor-binding domains (RBD) of spike proteins of SARS-CoV and SARS-CoV-2 show homogenous binding affinities with the ACE2 receptor.[11] RBD of (S) protein consists of six amino-acid residues that are crucial for the binding of RBD with the receptor. Comparative analysis revealed that 5 of these amino acid residues differ in SARS-CoV-2 (S) protein as compared to that of SARS-CoV.[11]

The entrance of coronavirus into the host target cell has been reported to occur through endosomal-membrane fusion triggered through the binding of S-protein of SARS-CoV-2 with ACE2 receptor of the host cell.[12] The transference of virus-receptor complex to endosomes actuated the fusion activity along with the cleavage of S-protein by proteases.[13] After the internalization, N-protein is primarily involved in the formation of Nucleocapsid and localization to the endoplasmic reticulum (ER) thus assisting assemblage and budding also.[14] Membrane protein being the most abundant protein, was found to be associated with the maintenance of the shape of the virus, interaction of all proteins of CoV, the formation of the viral envelope, and the release of VLPs.[15] The smallest protein, E-protein, has been investigated to be important in the replication, production, and maturation of the virus and its high expression within infected cells.[16] Moreover, it has also shown its participation in the assembly and budding of CoV from the Golgi-ER complex.[16]

In this review article, we have summarized previous and recent advancements related to the immune responses elicited in the host by SARS-CoV-2 infection which leads to deadly inflammatory cytokine storm in COVID-19.

Innate immune responses generated by SARS-CoV-2 infection

The first line of defense mechanism that includes non-antigen specific and natural immediate response is referred to as innate immune response.[17] The induction of inflammatory immune response mediated by macrophages and granulocytes in SARS-CoV-2 infected lungs cells has been reported. The host recognition receptors that differentiate viral stuff from host material and start immune responses through their activation have been investigated to include TLR-7, RIG-1, MDA-5, and cGAS-STING pathways.[18] The activation of recognition receptors triggers the type-1 IFN and inflammatory cytokines expression which has been demonstrated to restrict replication of virus by the activation of IFN stimulated genes. Researchers reported that an early immune response of IFN restricts viral replication efficiently while a delayed IFN response stimulated cellular damage in older persons.[19] The blockade of interleukin-6 (IL-6), IL-1 and tumor necrosis factor (TNF) production has been reported to be beneficial

against cytokine-release syndrome in patients suffering from COVID-19.[20]

The comparison of SARS-CoV-2 patients with previous pneumonia patients had shown a high expression of chemokines (Hyper-cytokinemia) in SARS-CoV-2 patients and stimulated expression of IFN-stimulated genes as well as inflammation-causing genes.[21,22] Moreover, an increase of over-expressed neutrophils and dendritic cells has also been reported in SARS-CoV-2 individuals.[23] It had also been revealed through transcriptional profiling of COVID-19 patients that an unsuitable inflammatory response assisted by decreased levels of interferons and high levels of chemokines confirmed a diminished innate-antiviral immune response caused by SARS-CoV-2.[24,25] Innate immune responses elicited by SARS-CoV-2 have been demonstrated to include reduced type-1 IFN response, activated hyper-inflammatory response, elevated neutrophil, and macrophage and induced Th1 or Th17 expression at initial stages of the virus.[26] Like SARS-CoV, COVID-19 has also been reported to suppress type-1 IFN production at initial stages and its transmission in asymptomatic individuals revealed slowed early innate immune response by the host against SARS-CoV-2.[27] An increased production of IgG antibodies and development of a T-cell response eliminate infected cells in COVID-19 patients.[28,29] Innate immune pathways like STAT-1 and MyD88 have been observed to partially control the pathogenesis of SARS-CoV-2.[30] During a host innate immune response study, it has also been scrutinized by various studies that human lung epithelial cells of SARS-CoV cease to trigger dendritic cell maturation and MHC class 2 complex expression.[31] In a comparative study between young and old SARS-CoV infected mice, elevated expression of TNFA, IL-6, CCL-2, CCL-3 and CXCL-10 has been investigated.[32] SARS-CoV infected human alveolar cells have been investigated to exhibit elevated levels of interferon- β, interferon- λ, cytokines, and chemokines during an innate immune response.[33,34] A potent innate immune response depends on type-1 IFN responses and pathways that eliminate viral replication further trigger an active adaptive immune response.[35]

Adaptive immune response to infection by SARS-CoV-2

The generation of neutralizing antibodies in patients infected with SARS-CoV has been detected upon and after the onset of illness against the virus.[36] The CD4+ and CD8+ T-cells along with other memory T-cells have been investigated to protect the host against the virus.[37] The identification of SARS-CoV-2 specific CD4+ and CD8+ T-cells has been reported with the recognition of type 1 and 2 HLA peptides in infected patients.[38] The expression of the spike-1 immunoreactive protein of SARS-CoV-2 in targeted cells can display viral proteins or markers and thus help in the development of an immune response.[39] B and T-cell epitopes have been identified as the prominent targets for generating immune responses against COVID-19 infection.[40] The analysis of adaptive immune response in SARS-CoV immunized mice has been reported to show elevated levels of CD80, CD86, and MHC class 2 molecules on mice dendritic cells (CD11c+).[41] Elevated numbers of some anti-inflammatory cytokines like IL-37 and IL-38 has been reported to successfully inhibit inflammation, class-2 MHC molecules, MyD88 pathway, TNF, CCL2, and IL-1β in SARS-CoV-2.[42] Release of several cytokines and chemokines during innate immune response has been demonstrated to trigger the activation of some other immune cells like neutrophils, macrophages, and dendritic cells to start an adaptive immune response to fight against SARS-CoV. It has been investigated that down-regulating the expression of CD8+ T-cell function in microglia and astrocytes helped in the control of CoV viral replication and secretion of neutralizing antibodies, also prevented its re-appearance.[43] In the case of SARS-CoV, the reduced number of CD4+ T-cells have been observed to slow down the production of cytokines and neutralize antibodies thus, failing to remove the viral

infection.[44] The release of cytokines and chemokines upon viral entry has been reported to trigger the production of cytotoxic T-cells (CD8+) and helper T-cells (CD4+).[45]

Mechanism of cytokine storm and involved cytokines

The SARS-CoV-2 infection generates cytokine storm in the lung due to uncontrolled secretion of inflammatory cytokines at the site of infection by immune cells (T-lymphocytes, dendritic cells, monocytes, macrophages) in the lungs. These inflammatory cytokines further cause acute respiratory distress syndrome (ARDS). According to a report published in Lancet states that ARDS is a major death factor in patients suffering from COVID-19. It is an immunopathological event that occurs after MERS, SARS, and SARS-CoV-2 infections.[46] ARDS is correlated with cytokine storm because immune effectors cells have been observed to release a large number of chemokines i.e. CCL2, CCL3, CXCL8, etc. and pro-inflammatory cytokines including; IFN-γ, IL-1β, IL-6, TGFβ, granulocyte-macrophage colony-stimulating factor, interferon-gamma-induced protein, MCP-1, MIP-1α, MIP-1β, PDGFB, and VEGF, etc., which results in the uncontrolled systemic inflammatory response and higher number of leucocytes. ARDS leads to cytokine storms, damages lungs and other multiple organs of the body which leads to multiorgan exhaustion and finally to death in severe cases.[47,48]

Interleukins

Higher levels of IL-1 and IL-2 in the serum of COVID-19 individuals have been observed and its elevated levels are correlated with the severity of the disease. Some therapeutic strategies, including mesenchymal cells (MCS), and other immunomodulatory drugs for the inhibition of IL-1 are under trial. TNF-alpha and IL-1-beta are major stimulators of the IL-6. In COVID-19 patients T-cell dysfunctionality, compromising the capacity of T cells against pathogens has been reported. Increased IL-6 level is related to a poor prognosis of the disease. Clinicians observed that inverse proportionality between elevated IL-6 levels and leucocytes count exists among patients admitted to ICU. The level of IL- 6 was remarkably elevated in patients who died than those who recovered from COVID-19.[49-51] Elevated secretion of IL-7 increases the production of pro-inflammatory cytokines and has a negative regulatory effect on TGF-β. Clinical researchers have indicated that the IL-7 level in COVID-19 patients is directly related to the severity of the disease. IL-10 blocks the production of pro-inflammatory cytokines; IFN-γ, TNFα, and IL-1β in different cells and arrest the maturation of dendritic cells by inhibiting the function and pathway of IL-12. According to various reports, clinicians have detected higher levels of IL-10 in patients suffering from COVID-19.[52-54]

Interferon-gamma induced protein-10

IFN-γ induces the secretion of CXCL10 (IP-10) which starts recruitment of leukocytes in inflamed tissues after binding with chemokine receptor-3 which results in inflammation leading to the deterioration of tissues. Elevated IP-10 levels have been observed in viral infections. Similarly, higher levels of serum IP-10 levels have been observed in patients suffering from SARS-CoV-2 particularly in those who were required intensive care unit admission which causes damage to lungs and disease severity.[55]

Interferon-gamma

IFN-γ can cause common cold-like symptoms, fever, headaches, dizziness, and fatigue. Interferons are pivotal molecules that act as antiviral agents in the initial stages of infection. The delayed release of IFNs in primary stages of MERS and SARS-coronavirus infections, obstruct the antiviral response of the body's immune system against these viral infections. In serum of COVID-19 patients, IFN-γ levels were elevated and this may be due to the activation of helper T-cells (Th1 and Th2).[56,57]

CONCLUSION

The outbreak of SARS-CoV-2 infection and the nature of COVID-2019 has demanded swift action in both basic immunological science and clinical research. In response to this, the scientific community has met with remarkable productivity in finding out the immunopathology of COVID-19. Within months, clinicians have done various analyses to investigate the host-pathogen interaction and immunology of SARS-CoV-2 infections. The violent response to SARS-CoV-2 infection is the uncontrolled release of proinflammatory cytokines and chemokines which results in induction of apoptosis and necrosis in epithelial and endothelial cells of lungs further leading to multiple organs dysfunction. Clinical researchers have found that the changes in the levels of these cytokines indicate the severity of the disease and its unfavorable prognosis. All these deteriorating conditions give rise to ARDS and finally death. Current evidence on adaptive immune responses strongly suggests that T-cell responses are crucial for the control of SARS-CoV-2. The possible therapeutic approaches are required to inhibit these outcomes, which include the use of antivirals, immunomodulators, immunosuppressant agents, and vaccines reducing the mortality and morbidity rate of patients suffering from COVID-19. Precise projection and targeted intervention using suitable cytokine storm antagonists, during the COVID-19 infection will be essential to improve the survival rate among patients and further investigations are required to verify various drugs and available vaccines.

AUTHOR'S CONTRIBUTION

MSA: Article writing
MSQ: Conception of idea
ZK: Review critically
TH: Editing
KA: Editing
AA Editing

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