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Extended Abstract

How much dreadful the cytokine storm appears after the entry of SARS-CoV-2 into the host?

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Abstract:

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is on its aggressive mode round the world so far accounting for approximately 600000 out of nearly 15000000 infected cases with extremely rapid transmission dynamics. The viral entry mediated by its unique spike (S) protein using the receptor-binding domain (RBD) for the attachment to the host angiotensin-converting enzyme receptor 2 (ACE2) acts as a cellular doorway for the virus to trigger the pathogenic events. Current write up shortly discussed about the host immunological response towards the SARS-CoV-2 entry. The viral entry is very much likely to initiate an immune response involving the innate immune cells to attack the virus. As the immune system recognizes the virus particles particularly the viral antigenic epitopes, the antigen-presenting cells (APCs) should process these antigens and present them both to the natural killer (NK) cells and the CD8+ cytotoxic T cells (Tc) in the context of major tissue histocompatibility (MHC) antigens which is in harmony to augment the signaling cells like the toll-like receptors (TLR-3, 7, 8) facilitating the recognition of the pathogen associated molecular patterns (PAMPs) under the innate immune system principally involving macrophages, dendritic cells, epithelial cells, neutrophils, and the natural killer (NK) cells.

The host innate immune response account for the huge production and migration of large amounts of pro-inflammatory cytokines and chemokines to the site of infection. These cytokines, like the interleukin (IL)-1β and IL-6 especially in case of COVID-19 cases, override and cause hyper inflammation with the consequent onset of high fever, myalgia and dry cough. Such a state can sustain towards the prolonged phase of hypercytokinemia (also called as macrophage activation syndrome) that encompasses a broad array of pro-inflammatory mediators like the IL-6, IL-1β, IL-8, tumor necrosis factor (TNF-α) together with the infiltration of inflammatory and the cells causing degranulation into the lungs, usually 7–10 days following the onset of the acute respiratory distress syndrome (ARDS). Interferons (IFNs) which is are signaling proteins play important roles in coordinating cellular immunity reactions to viral infections, thereby contributing to normal antiviral state. But when there is a cytokine storm, the levels of the pro-inflammatory cytokines Th1,Th2 and Th17 (T-helper cells) are all increased including IFN-α2, IFN-γ, IL-1 receptor antagonist (IL-1RA), IL2, 4, 7, 10, 12 and 17 (the IL-receptor antagonists), IFN- induced protein 10 (IP10), the monocyte chemo-attractant protein-1 (MCP-1), MIP1, the macrophage inflammatory proteins (MIP1), the granulocyte colony-stimulating factor (G-CSF), fibroblast growth factor (FGF-2), the macrophage colony-stimulating factor (M-CSF), the platelet derived growth factor subunit B (PDGFB) and the vascular endothelial growth factor A (VEGFA).

This is to be pondered that earlier in case of SARS-CoV infection, the accumulation of certain chemokines including CXCL8C, XCL10, CCL2, CCL3, and CCL5 was observed which was associated with the migration of NK cells. Decrease in the CD4+/ CD8+/ CD20+ lymphocytes, and in macrophages and NK cells within the spleen were also noticed. Besides, regarding the adaptive immunity, the human immune system usually relies on the B cells and the T helper (Th) cells particularly on Th1 and Th17; and concomitantly produces antibodies/ immunoglobulins (Ig) after exposure to an invading pathogen to fight off the remaining pathogen and to protect against future encounters. High titers of both IgM and IgG were detected in the blood of individuals infected in case of COVID-19 patients like the previous Middle East respiratory syndrome coronavirus (MERS- and the SARS corona viruses. IgM is associated with acute exposure (usually after the first week) to an antigenic challenge although they are not typically long-lasting. IgG is the second Ig to appear in blood and this occurs within 2-4 weeks following infection.

However, levels of IgG can remain detectable in blood for much longer than this. Detection of IgM and/or IgG suggests that a person has been infected in the past with SARS-CoV-2. However, there are challenges for patients who are at risk to make use of these B memory cells. T lymphocytes including both CD4+ and CD8+ subtypes and especially the NK cells are much lower than expected in the patients with severe cases of diseases (the fatal stage including the major organ failure together with ARDS) who have the underlying medical conditions like the abnormalities in the body mass index (BMI), obesity, D-dimer, older age, co-morbidities, diabetes, sequential organ failure assessment (SOFA), and diabetes. In addition, patients who usually have low lymphocyte count, chronic obstructive pulmonary disease (COPD), high vulnerability to the opportunistic infections are also at high risk of such cytokine storm which in turn leads to severe pneumonia, ARDS, kidney failure, etc. This is to be noted that besides S protein, the nucleocapsid (N) protein of SARS-CoV-2 is also involved in the viral pathogenesis by facilitating the viral transcription and replication. Indeed, analysing the pathogenic events along with the host immunity avoidance by the SARS-CoV-2 would be helpful for designing drugs on the basis of the appropriate target sites of the virus; and emphasizing the cytokine storm would increment the implementation strategy of the immunomodulatory agents and specific anti-virals in order to mitigate the viral infection as well as to decipher the transmission dynamics of the on-going COVID-19 pandemic.

In sum, the rapid spread of SARS-CoV-2 has forced all medical institutions worldwide to carry out research, prevention and control. All efforts are being made to slow the spread of COVID-19 to provide better public health recommendations and to develop timely diagnostics, therapeutics and vaccines. The above potential mechanisms are based on two previous outbreaks of coronaviruses and on current partial research with many new mechanisms still unknown. New treatments are being developed based on existing experience in combating viral infections. However, at present, treatment strategies for SARS-CoV-2 infection are only

supportive, and more importantly, there are no specific antiviral drugs for COVID-19. Therapeutic interventions targeting these pro-inflammatory cytokines and chemokines may help to alleviate adverse inflammatory responses, such as JAK-STAT pathway inhibition. Studies have found that there may be individual differences in susceptibility to cytokine storm. The innate immune response of healthy people.