Review Article

The possible immunopathogenesis of SARS-Cov-2 infection - A review of immune changes in patients with COVID-19

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ABSTRACT

A highly infectious outbreak of Coronavirus disease (COVID-19) caused by a new coronavirus - Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) was first officially reported in December 2019 in Wuhan, China which spread rapidly worldwide infecting millions of people in many countries. Although most of infected patients are asymptomatic or develop mild symptoms that usually recover with good prognosis, 10-20% of infected people especially old age and those with underlying medical co-morbidity conditions, develops severe disease with multiple organ failure, primarily respiratory failure and death. SARS-CoV-2 infection shares similar genetics, pathogenic, epidemiological and clinical features with two other viruses belonging to same coronavirus family that have caused serious infections over the last two decades i.e SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and MERS-CoV (Middle East Respiratory Syndrome Coronavirus) and pathogenesis and immune changes observed in these infections can be applied to this new pandemic in order to learn the imperative role of the immune system during the course of coronavirus infections and possible use of immunomodulatory intervention and immunosuppressive drugs in management of severe patients. As the immunopathogenesis of SARS-CoV-2 infection is still not clear and understanding this underlying mechanism which leads to severe form of disease is important for identifying effective treatment for critically ill patients, this article reviews the immunopathogenic changes observed in SARS-CoV-2 infection and identify the possible mechanisms by which it induces immune changes including cytokine storm, in order to provide a reference for the early clinical identification and management of severe form of COVID-19 infection.

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1. Introduction

Coronavirus disease 2019 (COVID-19) characterized by high fever, dry cough, progressive dyspnea, joint pains caused by a novel coronavirus officially reported first in December 2019 in Wuhan, China which then spread rapidly worldwide.¹ WHO has officially named the virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease as Corona Virus Disease 2019 (COVID-19) on Feb 11, 2020.^{2,3} As of May 2020 there were more than

6.27 Million confirmed cases of COVID-19 worldwide and more than 376 thousand infection-related deaths.³

SARS-CoV-2 is a enveloped, positive-sense, single-stranded RNA virus belongs to beta-coronavirus family like the other two other coronaviruses that have caused serious fatal infections over the past two decades, i.e SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and MERS-CoV (Middle East Respiratory Syndrome Coronavirus).^{4,5} Full Genomic characterization studies of this new virus have indicated that 89% nucleotide present in the viral genome match with bat SARS-like CoVZXC2.^{6,7} It also shares 79% of its genome with the human SARS-

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CoV virus and molecular analysis have reported the similarities between the spike shaped receptor-binding domains of SARS-CoV and SARS-CoV-2,⁵ which is the most immunogenic part of the virus and probably binds to the same Angiotensin converting enzyme 2 (ACE2) receptors present on the human cell surface to gain entry into cells, thus suggesting that a similar pathogenic mechanism is involved in both the viral infections.^{5,8}

COVID-19 disease is less fatal than SARS-CoV and MERS-CoV, as most of infected patients remain asymptomatic or develops mild symptoms like fever and cough that usually recover by symptomatic treatment, but up to 10-20% of infected persons especially old age and people with underlying medical co-morbidity conditions, develops a severe form of disease with multi organ failure, primarily respiratory failure, requiring intensive care unit (ICU) admission which may even leads to death.⁹ The severe form of the disease is characterized by interstitial pneumonia and the rapid development of acute respiratory distress syndrome (ARDS) or septic shock with high serum levels of acute-phase reactant proteins and features of the macrophage activation syndrome (MAS) like hyper-ferritinaemia and diffuse intravascular coagulation (DIC).^{8,10}

Recent studies have indicated a significant relationship between the severity of disease and the levels of proinflammatory cytokines and subsets of immune cell in the body.¹¹ Some studies even indicated that during the patients response to SARS-CoV-2, the immune dysregulation and the high level of proinflammatory cytokines could be the main cause of tissue injury but the exact pathophysiological mechanism of COVID-19 still remains largely unknown and understanding this underlying mechanism which leads to severe form of disease is important for identifying an effective treatment for critically ill patients. This article reviews the immunopathogenic changes observed in SARS-CoV-2 infection and the identify the possible mechanisms by which it induces various immune changes including cytokine storm, in order to provide a reference for the early clinical identification and management of severe form of COVID-19 infection.

2. Structural Features of SARS-CoV2

In order to understand the crucial role of the immune system during the course of COVID-19, it may be useful for first understand the structural features of SARS-CoV2. The genome of SARS-CoV2 is a positive sense, single-stranded RNA (+ssRNA) with 5'-cap structure and 3'-poly-A tail which is a typical genomic structure of Coronaviruses.¹² The initial genetic analyses of SARS-CoV-2 genomes demonstrated that this virus has evolved into two main types, the L type and S type. L type accounts to 70% of infection and is more aggressive and infectious in nature than S type which accounts for 30% of infection

and is more ancestral version.¹³ The genome of SARS-CoV2 like other typical Coronaviruses consist of six open reading frames (ORFs) and numerous accessory genes. 1/3rd of the genome encodes for major structural proteins like spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins, all of which plays a crucial role in the viral infectivity.¹² The S glycoproteins present on the surface are the receptor binding proteins which are responsible for the binding of virus to angiotensin-converting enzyme 2 (ACE2) on the human host cells leading to viral-host cell membrane fusion and the internalization of the virus.¹² The E protein is a small integral membrane protein and plays a role in assembly of virus particles, budding and Release of the virus from the host cell and it is also involve in viral pathogenesis.¹² The M protein is the most abundant protein component of the viral envelope, It has three trans-membrane (TM) domains, glycosylated NT ectodomain, and a CT domain that binds to the virus nucleocapsid to gives shape to the virions, it also promotes membrane curvature.⁹ The N protein is consist of an amino (N)-terminal (NT) domain and a carboxy (C)-terminal cytoplasmic tail (CT) domain and located within the core of the viral particle. Both domains bind to viral RNA to form the helical nucleocapsid. N protein also acts as an antagonist to the interferon pathway by regulating the signaling and synthesis of type I interferon (IFN), which is one of the most important response in the innate immunity to viral infection.⁹

3. The Immune Response in COVID-19

The outcome of any viral infection is basically determined by virus-host interaction and immunologic response of host to the virus. The effective antiviral responses of the host innate immunity and adaptive immunity, including the production of proinflammatory cytokines, the activation of CD4+ T-helper cells (Th cells) and CD8+ T(cytotoxic) cells, are essential for controlling the viral replication, check the spread of virus, inflammation and cleaning the infected cells.¹⁴ The precise immunopathogenesis of the SARS-CoV-2 is still not fully investigated, it would be useful get some knowledge from earlier researches done on SARS-CoV and MERS-CoV in order to understand the vital role of the immune system during the course of corona virus infections. SARS-Cov and MERS-CoV infection also causes acute respiratory diseases and are associated with high morbidity and mortality rates. These diseases are not only similar in their pathological terms, but also have striking similarity in terms of their clinical presentation and epidemiology.

3.1. Immune changes in SARS- CoV infection

The early hypothesis based on previous research on SARS- CoV suggested that the severity of SARS- CoV was due to cytokine dysregulation which was confirmed

subsequently by various findings. SARS-CoV infection induces abnormally low levels of type I interferons (IFNs), which is the part of the very early immune response to viral infections as they are secreted upon stimulation by viral pathogen-derived nucleic acids.^{5,15} Patients with SARS-CoV infection is noted to have high levels of pro-inflammatory cytokines and chemokines, associated with T cell depletion, pulmonary inflammation and extensive pulmonary tissue damage.¹⁵ In the acute phase of infection, sudden rapid decrease in lymphocytes count in peripheral blood was also noted, and both CD4+ helper T cells and CD8+ T lymphocytes counts were decreased.¹⁶ Chemokines, such as interferon-inducible protein-10 (IP-10) and monocyte chemoattractant protein (MCP-1) were profoundly expressed during the course of the disease and played a vital role in the development of pulmonary disease by causing accumulation of immune cells in the lungs parenchyma.¹⁷ An increased concentration of interleukin (IL)-6 was also observed which correlated with severity of disease. As the disease advanced, levels of IL-8 and TNF- α was observed to increase which peak in the early stage of recovery, while levels of MCP-1 were increased in the early stage of disease and decrease gradually as the disease progressed.^{18,19}

3.2. Immune changes in MERS-CoV infection

The clinical features of MERS-CoV infection, like that of SARS-CoV infection, ranges from asymptomatic cases to severe pneumonia with acute respiratory distress syndrome, septic shock, and multi-organ failure resulting in death.^{18,20} Like SARS, MERS-CoV also infects human airway epithelial cells, THP-1 cells (a monocyte cell line), human peripheral blood monocyte-derived macrophages and Dendritic cells, and induces a delayed but elevated levels of proinflammatory cytokines and chemokines.^{21,22} After MERS-CoV infection, plasmacytoid dendritic cells, but not mononuclear macrophages are induced to produce a large amount of IFNs. Serum cytokine and chemokine levels were found to be significantly higher in patients with severe form of MERS infection than in patients with mild to moderate MERS infection.²³ The elevated serum cytokine and chemokine levels in MERS patients are related to the high number of neutrophils and monocytes in the patient's lung tissues and peripheral blood, suggesting that these cells may play a role in lung pathology.^{23,24}

4. The Possible Immunopathogenesis in COVID-19

Even though the pathogenesis of COVID-19 is not fully understood, patients infected with SARS-CoV-2 show clinical and laboratory manifestations similar to SARS-CoV and MERS-CoV, a review on the studies done on these viruses can give a lot of information on the understanding the possible pathogenesis of SARS-CoV-2 infection. Based

on the review of published literature on clinical and laboratory observations of COVID-19 patients and we can postulate the possible immunopathogenesis of SARS-CoV-2 infection in humans.

4.1. Coronavirus entry and replication

Once the virus enters the body by passing through the mucous membranes of nasal and larynx mucosa, it then enters the lungs through the respiratory tract.¹ The virus then reaches Alveoli and infects the alveolar epithelial type II (AEC-II) cells by binding to angiotensin-converting enzyme-II (ACE-II) receptor by means of its spike (S protein) glycoprotein and then enters the cell cytoplasm. After entering into the cell, the viral genome (RNA) is released into the host cell cytoplasm and is translated into two poly-proteins and structural proteins, the viral genome then starts to replicate.²⁵ The newly developed envelope glycoproteins of the virus are then inserted into the membrane of the endoplasmic reticulum and the nucleocapsid is formed by the combination of viral genomic RNA and nucleocapsid protein. The viral particles then germinate into the endoplasmic reticulum-Golgi intermediate compartment.²⁶ The vesicles containing the virus particles then fuses with the host cell plasma membrane leading to release of the virus into the surroundings.²⁶ (As shown in the Figure 1)

4.2. Viral antigen presentation, humoral and cellular immunity

As soon as the virus enters the cells, its antigens are presented to the antigen presentation cells (APC), Antigenic peptides are presented by Major Histocompatibility Complex (MHC) or Human Leukocyte Antigen (HLA) which are recognized by virus specific cytotoxic T lymphocytes. The antigen presentation of the virus is primarily dependent on MHC-I molecules, but MHC II also contributes to its presentation.²⁷ Antigen presentation subsequently leads to activation of both humoral and cellular immunity response, mediated by virus specific B and T lymphocytes. As seen in other acute viral infections, the antibody response against the SARS-CoV-2 virus present with typical pattern of Immunoglobulin M (Ig-M) and Immunoglobulin G (Ig-G) production.²⁸ The SARS-specific IgM antibodies generally disappears at the end of 12 weeks, while the IgG antibody levels may last for longer duration.²⁸

The most efficient and rapid host response against the virus consists of the production of type I interferons (IFN α and IFN β) which forms an essential part of the antiviral innate immune system.²⁹ In the early phase of SARS-CoV-2 infection, the virus cause dysregulation of the interferons response which allows the virus to rapidly grow and spread to different organs in the body. Thus, the virus

Fig. 1: Possible mechanism of cytokine storm syndrome in COVID-19 patients. **1)** SARS- CoV-2 virus infects the alveolar epithelial type II (AEC-II) cells by binding to angiotensin-converting enzyme-II (ACE-II) receptor by means of its spike S glycoprotein **2)** Virus enters the host cell cytoplasm where it releases its RNA genome, begins to replicate, forms new viral particles and releases them. SARS-CoV-2 also invades alveolar macrophages and activates the innate immune system. **3)** Macrophages and virally infected dendritic cells and other innate immune cells capture the virus and in turn releases chemokines (mainly interferons) and cytokines like IL-6. **4)** The rapidly increased cytokines and chemokines then attract many other inflammatory cells causing them to migrate from blood vessels into the site of inflammation and these cells release additional chemokines/cytokines to amplify cytokine storm response **5)** This results in excessive infiltration of the inflammatory cells into lung tissue and thus leading to lung injury and respiratory failure.

acquire some time during the early phase of infection in order to establish itself in the host.²⁹ At the same time, the virus-induced chemokines like Interferon gamma-induced protein-10 (IP-10) and Interleukins attract the immune cells to the site of infection. These invading immune cells can themselves get infected and may produce even more chemokines and cytokines such as the proinflammatory cytokine like Interleukin-6 (IL-6) and also IFN- γ which will induce even more production of IP-10 and the other anti-inflammatory cytokine like TGF- β .²⁸ This combination of high virus replication followed by the massive production of activated immune cells and production of both pro-inflammatory and anti-inflammatory cytokines may result in a development of cytokine storm which leads to

severe and devastating alveolar and interstitial inflammation causing lung tissue damage and filling the alveoli with inflammatory exudates.²⁸ This eventually results in severe hypoxia and respiratory failure. This so-called 'cytokine storm syndrome' causes the most severe symptoms of the disease characterized by pneumonia, difficulty breathing, and organ damage.²⁹ Once the virus enters the peripheral blood causing viremia, it would attack the organs that express ACE-2 on their cell surface, such as heart, renal and gastrointestinal tract.³⁰ The cytokine storm syndrome can eventually progress to septic shock and multiple organ failure.³⁰

During the course of infection, in the early stage of disease, the leucocytes count in peripheral blood is normal

or slightly low, but lymphocytopenia is observed in some patients.³¹ Guan et al²⁶ described the clinical characteristics of 1,099 patients with laboratory-confirmed COVID-19 and Lymphocytopenia was observed in 82.1% of patients.²⁶ Similarly, in study done by Huang et al³² on 41 COVID-19 patients observed that ICU patients were more likely to have Lymphocytopenia (absolute lymphocyte count <1000 / μ L) compared to non-ICU patients. We suggest that lymphocyte reduction may occur early in the disease, which may affect antibody production in the patient. In severe type patients the lymphocytes were significantly reduced as observed in study done by Wang D et al³¹ on 138 Hospitalized Patients with SARS-CoV 2 infection where most patients with severe disease had marked Lymphocytopenia when compared to less severe cases. Thus lymphocytes counts in patients with COVID-19 might gradually decrease as the disease progress. The reason of significant lymphocyte reduction in severe type patients still remains unclear. The study done by Suxin Wan et al¹¹ on 123 hospitalized patients with COVID-19 showed the reduction of CD4 + T accounted for 52.90% in the mild group, and 95.24% in the severe group; the reduction rate of CD8 + T accounted for 28.40% in the mild group, and 61.90% in the severe group, indicating that T lymphocytes were more inhibited in severe patients. The percentage of B cell reduction was 25.49% and 28.57% and that of NK cell reduction was 34.31% and 47.62% in mild and severe group respectively. Besides this, IL-6 and IL-10 levels were also observed to be on higher side in severe patients compared to mild cases.¹¹

4.3. The cytokine storm syndrome and role of cytokine Interleukin-6(IL-6) in COVID-19

Cytokine dysregulation is an important finding noted in patients with COVID-19. Recent studies on critically ill patients with COVID-19 shows that, during the course of infection, the severe deterioration of health of some patients was closely related to dysregulation of immune response to the virus leading to an excessive and uncontrolled release of proinflammatory cytokines termed as 'Cytokine storm syndrome' in their bodies.³³ Data obtained from studies conducted on SARS-CoV-2 infected patients have shown that Acute Respiratory Distress Syndrome (ARDS) is the common finding observed in severe form of SARS-CoV-2 infection, as observed in previous Corona virus outbreaks SARS-CoV and MERS-CoV infections.³³ One of the main mechanism for development of ARDS is the cytokine storm syndrome, characterized by uncontrolled excessive systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines like IFN- α , IFN- γ , IL-1 β , IL-6, IL-12, IL-18, IL-33 and TNF- α and chemokines like CCL2, CCL3, CCL5, CXCL8, CXCL9, and CXCL10 by immune effector cells.^{34,35} Both pro-inflammatory cytokines (IL-1, IL-6 and TNF- α) and anti-inflammatory cytokines (IL-10 and interleukin 1 receptor

antagonist) levels are high in serum of patients experiencing cytokine storm.³⁴ Study done by Huang et al.³² also demonstrated that the levels of IL-2, IL-7, IL-10, TNF- α , G-CSF, IP-10, MCP178 1, MIP-1A were significantly higher in severe form SARS-CoV-2 infected patient requiring intensive care and admitted in ICU than those in non-ICU patients. (As shown in the Figure 2)

Thus cytokine storm will generate a violent attack of the immune system in the body causing ARDS and multiple organ failure ultimately lead to death in some of the severe cases of SARS-CoV2 infection, just like what was observed in SARS-CoV and MERS-CoV infection.³⁶ High levels of expression of IL-1 β , IFN- γ , IP-10, and MCP-1 have also been detected in patients with COVID-19 and these cytokines may activate the T-helper type 1 (Th1) cell response which generates series of immune responses.³⁷ Despite the activation of Th-1 cells, the total lymphocyte count is found to be low in some patients, suggesting that SARS-CoV-2 mainly infects lymphocytes. This lymphocytopenia is related to the severity of SARS-CoV-2 infection as observed in study done by Chen et al¹ on 99 confirmed cases of covid-19 where the absolute lymphocytes count where reduced in most of the patients.¹

IL-6 plays an important role in the cytokine storm and the serum levels of IL-6 in patients with COVID-19 correlate positively with the severity of the disease and it may be suggested that the serum level of IL-6 can be used to predict the prognosis of COVID-19.³⁸ Study done by Diao et al.³⁹ found that disease severity correlated with serum levels of TNF- α , IL-6 and IL-10. This study not only found that their ICU patients had lower CD4+ T cells and CD8+ T cell counts (especially, all of the ICU patients had low CD8+ counts), but also observed that TNF- α and IL-6 concentrations negatively correlated with total T cell, CD4+ and CD8+ counts. Similarly retrospective, multicenter Study done by Ruan Q et al.³⁸ on 150 confirmed cases of COVID-19 in Wuhan, China, showed high levels of serum ferritin and IL-6 in severe form of disease suggesting that high mortality may be due to hyper-inflammation reaction to the virus.³⁸ Similarly study done by Fang Liu et al⁴⁰ on 140 COVID-19 cases, demonstrated that the levels of IL-6, CRP, and procalcitonin (PCT) significantly increased in 67.9%, 65.0%, and 5.7% of patients on admission respectively and the levels of IL-6, CRP, and PCT was significantly higher in the severe group than in the mild group, which is consistent with the concept of 'cytokine storm syndrome' and suggesting that inflammatory factors played a crucial role in the disease progression from milder to severe form. Study done by Huang et al³² on 41 COVID 19 patients also showed that the serum levels of IL2, IL7, IL10, GCSF, IP10, MCP1 and TNF α were higher in ICU patients than non-ICU patients.

Based on the observations from above mentioned studies, dysregulated and/or exaggerated cytokine and chemokine

Fig. 2: The role of cytokine Interleukin-6(IL-6) in COVID-19: IL-6 shows significant pro-inflammatory properties and plays a crucial role cytokine storm syndrome as increased serum levels of IL-6 is correlated with respiratory failure and ARDS. It functions through two main signaling pathways: cis and trans. In cis signaling pathway, IL-6 forms a complex with the membrane-bound IL-6 receptor (IL-6R) and gp130 which then activates downstream the Janus kinases (JAKs) and signal transducer and activator of transcription 3 (STAT3). The activation of this signal cascade leads to multiple effects on the acquired immune system (B and T cells) as well as the innate immune system (neutrophils, macrophages, and natural killer cells) which contributes to CRS. In trans signaling, circulating IL-6 bind to the soluble form of IL-6 receptor (sIL-6R) and form a complex with a gp130 dimer on most somatic cell types. The resultant IL-6-sIL-6R-JAK-STAT3 signaling is then activated in cells that do not express mIL-6R, such as endothelial cells. This severely aggravates the “cytokine storm” through secretion of vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1 (MCP-1), IL-8, and additional IL-6, as well as reduced E-cadherin expression on endothelial cells. Secretion of VEGF and reduction of E-cadherin expression contribute to vascular permeability and leakage which participate in the pathophysiology of pulmonary dysfunction in ARDS.

responses by SARS-CoV 2-infected cells could play an important role in pathogenesis of COVID-19 disease leading to a more severe form of disease causing acute lung injury and ARDS. The based on the observations obtained from treating previous Corona virus infections like SARS and MERS shows that by reducing viral load through interventions in the early stages of the disease and controlling inflammatory responses through immunomodulatory drugs like IFN- λ , Corticosteroid, IL-6 antagonists like tocilizumab, Intravenous immunoglobulin (IVIG) and TNF blockers may act as effective measures

to improve the prognosis of SARS-CoV-2 infection. A therapeutic clinical trial on larger population might shed light on the effect of such immunomodulatory intervention on the morbidity and mortality of critically affected cases with COVID-19.

5. Conclusion

The COVID-19 pandemic caused by SARS-CoV-2 virus is spreading across the globe at an alarming rate. It has caused more infections and deaths as compared with

previous Corona virus infections like SARS- CoV or MERS-CoV, and its outcome is likely to be determined by the extent of the host immune system imbalance. The primary immune response is a positive response that leads to viral clearance in the majority of cases. However, in some cases, it may lead to the exaggerated secondary immune response characterized by excessive and prolonged cytokine/chemokine responses known as the cytokine storm leading to ARDS or multiple-organ dysfunction, which leads to physiological deterioration and death. In other words, it is the exaggerated immune response, or the immunopathogenic response, which is responsible for severe pneumonia and consequently respiratory failure and death. Timely control of the cytokine storm in its early stage through such means as immunomodulators and cytokine antagonists, as well as the reduction of lung inflammatory cell infiltration, is crucial to improve the success rate of the treatment and also to reduce the mortality rate of patients with COVID-19.

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7. Conflict of Interest

None

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