

Immunological Basis of COVID-19

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ABSTRACT

Currently major challenge for scientists is to cope with Coronavirus infection that alters host immune response in different ways. There is variability in immune response in diverse populations against this infection and particularly immunity of a certain population against SARS-CoV-2 is not clear. Many factors such as viral and host genetics that play crucial in this infection but immunological aspects are more important in infection and disease progression. Its different patterns of spread and severity needs timely focus to design strategies against this disease. This review sums up the concepts related to host immune response to SARS-CoV-2, cellular and humoral immunity, cytokines storm and immunization against COVID-19.

KEYWORDS: Coronavirus, COVID-19, SARS-CoV-2, Immune response.

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INTRODUCTION

Start of 2020 has become an exceptional and unforgettable memory due to novel virus infection that abolished health and economic system of the world. This virus is very similar to the coronavirus that was cause of Severe Acute Respiratory Syndrome in 2003; thus, it was given name of SARS-CoV-2 by the World Health Organization (WHO), and disease caused by this virus is known as COVID-19.¹ In December 2019, the epidemic originated from Wuhan, China, and transmitted to all over the world. WHO announced COVID-19 as global pandemic that is potentially more hazardous than terrorism.² Due to difference in host immune response, the variability in infection the severity of

disease in diverse population is different. The immunological changes, antibodies level, HLA variants, cytokines levels, functions of B cells and T cells are key players in immunity against SARS-CoV-2 and these immune modulators may play important role to combat COVID-19.

Human beings commonly have not specific immunity against this virus and so human population is at risk of infection with this novel virus. SARS-CoV-2 initiates host innate immune system when recognized by Pattern Recognition Receptors (PRRs) including Toll-like receptor (TLR).³ The virus induces inflammatory cytokines and production of interferons that restrict the virus propagation.⁴ The adaptive immune response plays its role against SARS-CoV-2, B cells are induced by CD4⁺ T cells to produce specific antibodies, and CD8⁺ T cells kill cells infected with virus. Proinflammatory cytokines are produced by T helper cells that help the immune cells to fight against viral infection.⁵ SARS-CoV-2 can hinder T cell functions by T cells depletion. In some cases of COVID-19, cytokine storm arises by rapid response of the immune system that is a systemic response by the production of inflammatory cytokines

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including TNF α , IL-6 and IFNs. These cytokines provoke immune cells to produce free radicals leads severe damages to the lungs, multi-organ failure and even death.⁶⁻⁸ Immuno-suppression is vital for the treatment: corticosteroids and anti-IL6 monoclonal antibody are used for this purpose with some limitations.⁸⁻¹⁰

Antibodies recognize and neutralize unique molecules of the pathogens against which they are formed. Therefore, passive immunization is the treatment of patients with the plasma of patients who have recovered from the same infectious diseases.¹¹ Besides therapeutic effects, antibodies can stimulate the immunity and may lead to lethal cytokine syndrome.¹² Thus, better option is to get B cells from COVID-19 patients who recovered from disease and categorize effective antibodies against proteins of the virus that are crucial for virus assembly or replication. Hence by monitoring antibodies level and immune responses in patients, use of antibodies and B cells for therapeutic purpose can be suggested.

Host Immune Response against SARS-CoV-2 and T Cell Depletion

Coronaviruses use their surface protein (spike protein) to enter a cell by binding to the ACE2 receptor on the host cell membrane. Antigen-Presenting Cells (APCs) engulf the viral particles and present the viral antigenic peptides complexed with the Major Histocompatibility Complex (MHC) class I and class II proteins to CD8⁺ and CD4⁺ T cells respectively (13). Conventional Dendritic cells (DCs) scan the body for dangerous invaders. When there is an inflammation triggered by SARS-CoV-2, a new type of DC emerges. This newly discovered DC called the inflammatory type 2 conventional DC, or inf-cDC2 has some of the finest characteristics of the monocytes, macrophages, and conventional DCs, to induce the best form of immunity. In respiratory viral infection by SARS, they optimally prime CD4⁺ and CD8⁺ T cell immunity.¹⁴

T cells help B cells in their differentiation to plasma cells, which produces antibodies specific to viral substances (peptides). To limit the infection, an antibody fully blocks the virus from infecting the host cell and thus provide defense at the later stages of the disease and also prevents re-infection in the future.¹³ CD4⁺ T cell directs the overall

adaptive immunity while CD8⁺ T cells (cytotoxic T cells) clear and destroy the viral infected cells. Since an efficient defense against the viral infection depends on the activation of CD8⁺ T cells, hence enhancing the numbers and function of T cells in COVID-19 patients is important for recovery. However, in the SARS-CoV-2 infection, different studies show that there is a significant decrease in the cytotoxic and helper T cell counts, which may result in decreased propagation and persistence of T memory cells in the COVID19 survivors.¹⁵ Excessive inflammatory reaction characterized by the rapid production of cytokines (IL-6, IL-10, and TNF- α) in large amounts is a hallmark of SARS-CoV-2 infection.^{7,8} This may contribute to a decrease in the number of T cells as it has been reported that the numbers of total T cells, T helper, and cytotoxic T cells are negatively correlated to the level of, IL-6, TNF- α , and IL-10, respectively. These cytokines are not produced by T cells; however, they may enhance apoptosis and necrosis of T cells leading to T cell exhaustion.¹⁵

TNF- α is a pro-inflammatory cytokine that may enhance T cells apoptosis by binding TNFR1 receptor, whose expression is enhanced in the matured T cells. TNF- α may be at once involved within the reduction of T cells in COVID-19 patients. IL-6, when directly and transiently produced in reaction to infections and tissue injuries, contributes to host defense through the stimulation of acute-segment responses.¹⁵ Dysregulated and chronic synthesis of IL-6 had been shown to play a pathological role inside the continual inflammation and infections thus it may also be a contributing factor in the reduction of T cells in COVID-19 patients.^{8,9} IL-10 an anti-inflammatory cytokine, not only prevents T cell propagation but can also contribute to T cell exhaustion. COVID-19 patients are stated to have a high level of IL-10, while also exhibiting high expression of PD-1 and Tim-3 exhaustion markers on the surface of T cells.¹⁵ This shows that IL-10 might be directly involved in the reduction of T cells. The use of effective antiviral remedies to stop the development of T cell exhaustion in COVID-19 patients may thus be vital to their recovery.

Cytokine storm and COVID-19

The SARS-CoV-2 is recognized by ACE-2 receptors,

then after internalization it starts replicating inside the cell.¹⁶ When newly assembled virus particles are released from the infected cell, it also results in release of damage associated molecular patterns (DAMPs) such as ATP, viral RNA, HMGP-1, and host DNA into the extracellular matrix. DAMPs are recognized by neighboring epithelial cells and alveolar macrophages. These cells secrete inflammatory cytokines such as IL-6, IP-10, MIP α , MIP β , MCP1 and results in subsequent recruitment of T cells, monocytes and macrophages at the site of infection. T cells secrete IFN- γ to clear viral infection. Accumulated T cells, monocytes and macrophages also give a positive feedback to enhance the production of proinflammatory cytokines.^{16,17} Infected cells and viruses are cleared rapidly in individuals having a healthy immune system. Neutralizing antibodies inactivate viral S protein and alveolar macrophages phagocytose the neutralized virus.^{18,19,17} CD4⁺ and CD8⁺ T cells orchestrate cell mediated immunity and kill viral infected cells. Main cytokines that mediate cellular immunity and viral clearance are IL-15, IFN α , IFN β , IFN- γ , IL-12 and IL-21. Minimal inflammation and lung damage happen during healthy immune response.^{6,21,25}

However, in some patients an aberrant immune response occurs that results in hyperinflammation of lungs. Several host factors such as age (>60 years), hypertension, smoking, diabetes, coronary heart disease have been implicated in immunopathogenesis of COVID-19.^{20,21,25} Due to unrestrained infiltration of monocytes, macrophages and T cells, several cytokines such as IL-6, IP-10, IFN- γ , IL-10, IL-17A, IL-2, G-CSF, GM-CSF, MIP1 α , and TNF α are secreted in high quantities and constitute the cytokine storm.^{6,7} Cytokine storm cause multi organ pathologies including heart, liver, and kidney.^{17,26} Specifically, increased levels of TNF α can cause septic shock and multi-organ failure.³⁰ It has been observed that level of IL-6 continues to increase in these patients, and it is more elevated in non-survivors than survivors.²⁵ About 28% fatalities in COVID-19 patients are due to the consequences of cytokine storm and sepsis.²⁹ Reduced peripheral lymphocytes, increased levels of IL-6 and abnormal coagulation parameters are hallmark of critical cases.^{7,29} Cytokine storm is evident at third week of COVID-19 infection. Immunosuppression by

targeting IL-6 or IL-6R using blocking antibodies or antagonists can have benefits. Recent evidence has suggested that blood purification therapy can also have potential therapeutic benefits in removing pathogenic antibodies and cytokines.^{17,30,31}

Vaccines as a Therapeutic Modality for COVID-19

A vaccine provides adaptive immunity against a certain pathogen or a disease. Vaccines are classified on many criteria; on the basis of intended use, and it can be preventive or therapeutic. Preventive or prophylactic vaccines are meant for prevention of future infection and these are usually available in the form of either live attenuated/killed whole virus or a component of that pathogen.³² Therapeutic are meant to treat a particular disease or infection. Both types of vaccines are dire need of time to combat SARS-CoV-2 infection, for this a complete understanding of protective immune response against SARS-CoV-2 is required but currently we know very little about it.³³ Therapeutic vaccines usually contain preformed antibodies against that particular pathogen. These antibodies can be produced *in vitro* by monoclonal technique or from the serum of immunized animals or infected persons. The former requires extensive knowledge of antigenic structures of that pathogen whereas both the above-mentioned techniques require isolation and inoculation of virus. Data of immunizations vectored vaccines as well as injection of antisera from immunized animals or infected persons have suggested protection in animal models of infections.³⁴ In some countries passive transfer of antibodies from recovered COVID-19 patients has shown promising results but these studies are very few in number and they are limited by small sample size.³⁵

Gene based (nucleic acid) and protein-based (Recombinant) vaccines are assembled as particles that are manufactured *in vitro*. These vaccines can be developed rapidly and easily adapted for large scale manufacturing.³⁶ It is absolutely necessary to develop a vaccine rapidly to prevent COVID-19 and it is critical to define the stakes and potential hurdles for this so that regulatory and medical decisions can be made for benefit after risk calculations. There is another key question that

protection against SARS-CoV-2 will occur through effective vaccine or by virus persistence so that most of the people develop immunity (herd immunity). This herd immunity can diminish pandemic spread of virus but these repeated waves of infection will lead to high mortality due to SARS-CoV-2.³⁷ Therefore, the benefit of developing an effective vaccine is very high, and even greater if it can be deployed in time to prevent repeated or continuous epidemics.

CONCLUSION

This review elaborates pathways and mechanism of SARS-CoV-2 infection and immuno-pathogenesis of COVID-19. At large, SARS-CoV-2 infection involves both innate and acquired types of immunity. During the initial phases of infection, innate immune system reacts against viral infection by producing type-1 interferons and other cytokines. In a number of patients, cytokines storm occurs, which lead to uncontrolled inflammation and irreversible tissue necrosis especially in lungs tissue. It causes irreversible damage to the alveolar tissues leading to death due to severe acute respiratory syndrome type-2. To combat SARS-CoV-2 infection effectively, production of specific neutralizing antibodies by adaptive immune system is necessary. Hence research should be focused to boost up adaptive immune response which is needed to develop preventive and therapeutic vaccines.

CONFLICT OF INTEREST

None to declare.

FINANCIAL DISCLOSURE

None to disclose.

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Author's Contribution

SJ: Conception and design of work, revising manuscript critically for important intellectual content

RT, FS, KJ, MK: Acquisition of data, drafting of manuscript, revising manuscript critically for important intellectual content

NA: Conception and design of work, Final approval of the manuscript.