Immune Response to SARS-CoV-2 Infection

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Abstract: In December 2019 a new type of coronaviruses appeared in China and named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the disease associated with this virus is called Coronavirus Disease 2019 or COVID-19. Currently, COVID19 is the main global health threat. In this review, we focus in the current knowledge of immune response to SARS-CoV-2. Dysregulation of immune system, such as elevation levels of proinflammatory mediators and their roles in disease progression and pathogenesis as well as imbalance between innate and adaptive immune cells, are discussed in this review.

Key words: Innate immunity, adaptive immunity, coronavirus, COVID-19, SARS-CoV-2, Immune response.

Introduction
Coronaviruses are enveloped viruses with a single-stranded RNA. The genomes size is about 30–32 kb (1,2). The first human coronavirus was reported on 1966 by Tyrrell and Bynoe, named B814 (1,3). In the same period, Hamre and Procknow reported another strain of human corona virus called 229E (3,4). One year later, McIntosh et al reported multiple strains of human respiratory tract virus named as OC strains (e.g OC43) (5). In 1975, this new group of viruses has been given the name coronavirus, because of crown-like shape (6).

In 2002, a new form of human pathogenic corona virus was reported in China and named Severe Acute Respiratory Syndrome Corona (SARS-CoV). This virus was reported in twenty-nine countries around the world (7,8) and a total of 8098 individuals were infected with this type of virus with total fatalities of 774 (9). It was suggested that transmission of SARS-CoV is primarily from person to person via respiratory secretion but exact mode of transmission still unclear. The possible reservoirs for this corona virus were reported to be Himalayan palm civets and raccoon dogs (7,10).

Since 2003, six new human coronaviruses have been discovered including NL63 (11), NL (12), New Haven coronavirus (HCoV-NH) (13), HKU1 (14), Middle East Respiratory Syndrome (MERS) (15) and SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19) (16,17).

The SARS-CoV-2
The SARS-CoV-2 is closely related to SARS-CoV, both are belonging to beta-coronavirus genera (1). The virion of SARS-CoV-2 is about 50-200 nm in diameter, consists of four main proteins; the first three protein (spike (S), envelope (E), and membrane (M)) are located on the envelope of the virus and the fourth one is located on the nucleocapsid (N). The S protein facilitates the entry of the virus into host cell, after binding to a specific receptor on the host cells. This receptor has been identified as Angiotensin-Converting Enzyme 2 (ACE2), expressed by many cell types including cells of lungs, kidney, heart, arteries, intestines(1,2,18,19) and immune system (18,20).

Although the transmission mode is still not clear yet, but it was suggested that the virus can be transmitted through coughing, sneezing and close breathing from an infected individual or by hand after touching contaminated objects with the virus (21). SARS-CoV-2 infection is initiated by the interaction of the viral S proteins with ACE2 on host cells. After viral entry into the target cells, viruses undergo sequential events of RNA replications that eventually lead to dysfunction of infected cells. (1,2).

The most common symptoms of COVID-19 are pneumonia, fever, dry cough, tiredness and dyspnea (1,2). It has been shown that the mortality rate increases with increasing age or presence of co-morbidity such as diabetes mellitus (DM) (22). This can be attributed to the efficacy of the immune system, but this conclusion still premature yet.

Current available data indicates involvement of both innate and adaptive immune system components in the pathogenesis of COVID-19, including interferons (IFNs) response, high levels of circulating proinflammatory cytokines, lymphopenia, lymphocytes imbalance and extensive pulmonary infiltrates of mononuclear cells (1,2,22). This review focuses on immune response to SARS-CoV-2 infection.
Innate Immune response to SARS-CoV-2

To date, studies on the innate immune response to SARS-CoV-2 are still limited. However, findings from SARS-CoV may provide evidence for immune response to SARS-CoV-2 because of shared sequence homology between these two strains (1,2).

The innate immune components that may contribute to viral immune response in respiratory system includes soluble proteins such as IFNs, surfactant proteins that bind to viral particles and leukocytes (e.g alveolar macrophages, and natural killer (NK) cells) that engulf and kill invaders by using Pattern Recognition Receptors (PRRs), these receptors sense molecular patterns on pathogens, cause cell activation and cytokines and chemokines production, which induce an antiviral response. PRRs can be found on the cell surfaces or in the cytoplasm of variety of cells including cells of immune systems such as macrophages and T cells. Example of cytoplasmic PRRs that can recognise viral molecular pattern including RIG-I (Retinoic acid-inducible gene 1) and MDA5 (Melanoma Differentiation-Associated protein 5), collectively known as the RIG-I-like receptors (RLRs), along with endosomal Toll-like receptor 3 (TLR3) and TLR7. Activation of these receptors by RNA viral recognition induces type 1 IFNs response (23-25).

Type I IFNs response is mediated by a group of interferons including IFN-α along with IFN-β, IFN-γ, IFN-αo, IFN-ζ, IFN-τ, and IFN-ε. These cytokines are rapidly produced after PRR engagement, subsequently, influence development of immune responses to infections and promoting generation of effectors and memory T and B cell (24-27). Type II IFNs immune response is mediated by IFN-γ, predominantly produced by NK cells during viral infection, and has been shown to inhibit viral replication (26). In human, Type III IFN immune response is facilitated by IFNλ1(IL-29), IFNλ2 (IL-28A), IFNλ3 (IL-28B) and IFNλ4 (27). It has been shown that IFNs have effective antiviral responses and can reduce the excessive production of proinflammatory cytokines such as Tumour Necrosis factor (TNF), interleukin (IL)-1β, IL-6, IL-12, and IFN-γ and chemokines such as IL-8, MCP-1 and IP-10. These cytokines are a common complication of respiratory infections caused by influenza A, SARS-CoV and MERS-CoV (24-29).

In case of RNA viruses, these pathways (in particular type I/III interferons) are initiated through the engagement of both cytoplasmic RLRs and cell membrane PRRs (e.g TLRs). Engagements of these receptors trigger downstream signaling cascades eventually activate secretion of proinflammatory cytokines such as TNF-α, and IL-1β. IL-1 Receptor Antagonist (IL-1RA) IL-6, IL-7, and IL-18 (23,25,27).

Evidences from SARS-CoV (30), MERS coronavirus (31) and recently SARS-CoV-2, IFN-I response effectively able to reduce CoV infection (32,33). Interestingly, invitro study showed that SARS-CoV-2 is more sensitive to IFN-I/III than SARS-CoV-1 (32).

Raised levels of cytokines and chemokines including: IL-1β, IL1RA, IL-2, IL-6, IL-8,IL-10, IL-17,TNF-α, IL-18, CXCL2, CXCL9, CXCL16, CCL2, CCL3, G-CSF, GM-CSF, and MCP1, were observed in COVID-19 patients (34-39). These proinflammatory cytokines and chemokines may be the primary players on the pathogenesis, hyperinflammation and massive pulmonary infiltration of inflammatory cells (neutrophils, monocytes/macrophages) seen in COVID-19 patients and correlated with disease severity (34-38).

Recent studies showed that innate immune cells such as macrophages and dendritic cells play a central role in the inflammatory progression in COVID-19 patients (35-37). Type 1 macrophages (M1) respond to foreign substances via PRR and produce inflammatory molecules that can eliminate pathogens, whereas Typ2 macrophage (M2) triggers release of anti-inflammatory cytokines, which limit inflammation and promote tissue repair. Dendritic cells are known as a typical antigen presenting cells that involve in T cell activation. Hyperactivation of these cells can be damaging to the host (35-37). Moreover, the above cytokine profiles observed on COVID-19, show similarities to those observed in macophage activation syndrome (36,37,38). Thus, it can be concluded that dysregulated activation of macrophages is the main cause of massive production of inflammatory cytokines and chemokines (which leads to cytokines storm) that was detected in COVID-19 patients (36,37,38). Therefore, inhibition of macrophages activation and blockades of these pro/ inflammatory cytokines such as IL-6 (36) and IL-1β may provide an effective treatment for COVID-19.

Virgilio et al suggested that macrophage can be inhibited via P2X7 receptor (P2X7R) (40). Indeed, this suggestion is very valid, hence this receptor is expressed by mononuclear cells. Activation of this receptor triggers downstream-signaling cascades, resulting in profound production of proinflammatory cytokines, including IL-1β. Moreover, we and others demonstrated that
polymorphism at position 1068 and 1513 in the P2X7R gene might contribute to the pathogenesis of RA via accelerated production of proinflammatory cytokines (41,42). This finding may be applicable to COVID-19 patients, hence viral infection may cause a significant increase in ATP, a P2X7 ligand (43).

The complement proteins are considered as effective arm of innate immune system, activation of these proteins contributes to acute and chronic inflammation. Similarly, to cytokines and chemokines, hyperactivation of complement system may lead to anaphylactic shock and multiple organ failure (44,45). Several studies reported that complement system plays a key role in the pathogenesis of COVID-19 (45).

Moreover, postmortem analysis showed that elevated level of complement components mannose-binding lectin (MBL), C4, C3, and the terminal membrane attack complex C5b-9 in alveolar epithelial cells. Serum level serum C5a in COVID-19 patients have been found to be elevated (45,46). Histochemical analysis of kidney biopsies of COVID-19 patients revealed a strong C5b-9 complex deposition on kidney tubules demonstrating that complement system may contributes to the kidney failure in COVID-19 patients. Nevertheless, other innate immunity inflammatory markers such as C-reactive protein, ferritin, D-dimers and procalcitonin are found to be elevated in COVID-19 patients (38,47). CRP and procalcitonin are associated with high risks of mortality and organ malfunctions (48).

**Adaptive immune response to SARS-CoV-2**

It is yet unclear whether humoral response or cell mediated immunity of the adaptive immunity confers the most protective immunity in COVID-19 patients. Several recent studies showed dysregulations of adaptive immune response in patients with COVID-19(35,38,49-52). Several studies showed that SARS-CoV-2 infection alters CD4+ and CD8+ T cells proportion, T regulatory cells and neutrophil-lymphocyte-ratio, particularly in severe cases of COVID-19 (38,49). Moreover, total lymphocytes, CD4+ T cells (T Helper cells and regulatory T cells), CD8+ T cells, NK cells, monocytes, eosinophils and basophils have been shown to be decreased in COVID-19 patients, and severe cases had a lower level than mild cases (36,38). Moreover, the expression of IFN-γ by CD4+ T cells, CD8+ T cells and NK cells tended to be lower in severe cases than in moderate cases with increased expression of CD94/NK group 2 member A (NKG2A) receptor. However, this abnormality is restored after recovery (53-56). Neutrophil lymphocyte-ratio (NLR) in COVID-19 patients has been found to be imbalanced and correlated with the severity of the disease (38,49). Moreover, it was suggested that NLR and changes in the count of lymphocyte subsets can be used as diagnostic markers for early screening of critical illness (38).

Disproportion of naïve versus memory T cells in favor of Naive T cells was also reported. This scarcity of immunological memory development after natural active immunity can be implicated in the complexity of vaccine development for COVID-19 (38,53,54). Changes in humoral immune response in COVID-19 patients were also reported. It has been shown that high level of plasma cells and decreased level of naïve B cells was observed in COVID-19. These changes also affected novel B cells receptors (BCRs) including’s IGHV3-23 and IGHV3-7, and isotypes IGHV3-15, IGHV3-30, and IGKV3-11 (55,57).

Based on recent studies, antibodies to SARS-CoV-2 develop between 6–15 days after infection (57) and may remain over the course of seven weeks (58), which is much shorter period in comparison to SARS-COV-1 infection (52).

**Concluding Remarks**

- Current knowledge about immune response to SARS-COV-2 appears to be different from immune response in the other coronavirus infections.
- Components of innate and adaptive immune response seem to be key players on the pathogenesis of COVID-19.
- Proinflammatory cytokines, chemokines and complement pathways mediate hyperinflammation and severity of COVID-19.
- Blocking of these inflammatory processes could be a promising therapeutic approach for COVID-19.

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