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Literature Review

COVID-19 and Human Immune Response: A Literature Based Review

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Abstract: Currently, the world is facing the COVID-19 epidemic, a disease caused by SARS-CoV-2. Emerging body of molecular evidences suggested a similar path to SARS and MERS viruses. A viral particles cascade enters into the human body through eyes, nose, and mouth, few of these viral particles reaches to the lower respiratory tract through breathing and here their spike protein act like a key and lock into epithelial cells which are the air sacs in lungs. SARS-CoV-2 is undetectable for a longer period of time than many other flu and coronaviruses. Once they entered inside body, they overtake the cell's machinery, replicate, multiply and infect the adjoining cells. All the viruses have a tell-tale signature on the surface known as antigens, identifying these antigens is what activate the immune system by producing the antibodies. Researchers have shown that a wide range of immune cells that react to SARS-CoV-2 and helps in recovery could be helpful in the development of potential vaccines.

Keywords: COVID-19; SARS-CoV-2; SARS; Immune cells

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1. Introduction

About century after the emergence of the pandemic of influenza of 1918, we now appear to be experiencing a new epidemic. The eruption of the new COVID-19 disease (SARS-CoV-2) has spread to every landmass, prompting us to continue living with this disease for a prolonged period, perhaps. Researchers and clinicians have learnt a great deal about 2019 coronavirus outbreak, COVID-19 and its pathological processes [1]. Not all individuals susceptible to COVID-19 become diagnosed and not all affected people experience significant respiratory illness. This widespread catastrophe is partially clarified by the existence of viral transference; the median incubation period from COVID-19 infection to the onset of indicative dyspnea varies from 4 to 7 days, providing a wide transmission time span in which patients have little signs [1, 2]. Furthermore, several infected patients stay completely symptom free however, are completely able of spreading the infection [3, 4]. The outbreak may then be approximately split into three phases: phase I, a symptomless incubation phase with or without observable infection; phase II, a non-serious indicative cycle with the existence of infection; phase III, an extreme respiratory indicative level with a significant viral load [5]. When seen from a perspective of prevention, the individual in phase 1 who are the covert carriers, are the least manageable because they are not identified as the virus-carrier and yet are spreading the virus without their knowledge [4].

To date, no 100% authentic vaccinations or appropriate medications have been approved for the prevention or treatment of COVID-19 and the existing routine care is focused on supportive treatments. Therefore, immediate inquiries are required to produce therapeutic and preventive medicines, centered on the swift and global dissemination of the virus. Treatments that resolve the immunopathology of infection of COVID-19 have been a significant priority in this regard[6]. Particularly, although the first line of protection against viral infection is a well-coordinated and fast immune response, severe

inflammatory innate reaction and disrupted responsive host immune protection may result in damages to tissues both at the systemic level as well as the entry site of virus. Consequently, considering the central function of the immune system in COVID-19, a better knowledge of the process behind dysfunction of immune system may offer us insights into the medical treatment of extreme cases and to avoid the change from moderate to serious phases.

2. Two-Phased Immune Response Triggered by COVID-19

It is clinically seen that COVID-19 generally produces two phased immune responses. A strong adaptive immune response is necessary during non-severe and incubation stages to eradicate the infection and avoid the disease from progressing into serious stages. Thus, approaches to improve the immune response (pegylated IFNα or anti sera) are definitely essential at this point. In order to establish an endogenous defensive immune response at incubation and non-severe levels, the host has to be in a healthy condition and must have an adequate genetic history (e.g. HLA) that induces strong antiviral resistance. Individual differences in the immune responses to pathogens is known to be contributed by genetic variations[7]. Nevertheless, when a defensive immune response becomes damaged, viruses can spread and significant tissue damage can occur, particularly in organs such as kidneys and intestines which have higher ACE2 expression. The defective cells cause latent lung inflammation, which is primarily regulated by pro-inflammatory granulocytes and macrophages. At the severe stage, inflammation of the lungs is the main source of life-threatening respiratory problems [8].

Numerous reports demonstrate major alterations in both the adaptive and innate immune systems of patients with COVID-19. Lymphocytopenia, specifically, and a variation of total neutrophils are typical key features which tend to be closely associated with seriousness of illness and death [9, 10]. A significant decline in absolute rates of circulating CD8+ cells, CD4+ cells, B cells and natural killers (NK) cells followed by a reduction in basophils, monocytes and eosinophils was recorded in patients with extreme COVID-19 [11]. Moreover, the serum rates of pro-inflammatory cytokines have been seen to be substantially elevated in individuals with severe COVID-19 [12]. While there has been no clear proof of chemokines and pro-inflammatory cytokines engagement in COVID-19's lung pathology, in COVID-19 infected patients, a rise in serum cytokine and chemokine rates and an increase in neutrophil-lymphocyte ratio is seen to be associated with disease intensity and negative effects, indicating a potential role for hyper inflammatory reactions in the COVID-19 pathogenesis [11].

In addition, a retrospective longitudinal analysis found that COVID-19 patients had increased serum rates of procalcitonin and high-sensitivity C-reactive protein (Hs-CRP), two main inflammation indicators correlated with high mortality rates and organ injury incidence [13]. In another retrospective analysis involving a population of 452 COVID-19 patients, participants with extreme COVID-19 symptoms displayed a slightly lower number of overall T cells, both supporting T cells and suppressing T cells [11]. Naïve and memory T cells are two important components of immunity. Equilibrium is vital to holding a defensive answer successful. Dysfunction in their balance may contribute significantly to hyperinflammation. On the other hand, a decrease in memory T cells may be implied in COVID-19 recurrence, as several episodes have been observed in recovered COVID-19 instances[9, 14].

3. Cytokine Storm

COVID-19 infected individuals who are in severe stage are seen to be affected by Cytokine release syndrome (CRS). Because lymphocytopenia is frequently observed in serious COVID-19 patients, the virus-induced CRS needs to be regulated by leukocytes besides T cells, as in patients undergoing CAR-T therapy; a large count of white blood cells

is normal, indicating it as a specific prognostic marker for COVID-19 in combination with lymphocytopenia. The accumulating of clinical data from serious COVID-19 patients indicates that significant serum level changes in many cytokines play a crucial role in pathogenesis of COVID-19 [12, 15]. One of the factors causing inflammatory processes and contributing to the leakage of plasma, diffusion of vascular coagulation and permeability of vesicles in COVID-19 infected patients is seen to be associated with hypercytokinemia which is called the cytokine storm [8]. Moreover, based on Murray score, 15 cytokines were identified by a study done with a small group of COVID-19 patients to be associated with injury of lungs (IFN-α2, IFN-γ, IL-1ra, IL-2, 4, 7, 10, 12 and 17, chemokine IP-10, as well as G-CSF and M-CSF) [16].

Past literature also shows that the cytokine storm seen in COVID-19 closely relates to Cytokines Release Syndrome (CRS) which is primarily triggered by viral infections and is a form of acute inflammatory response syndrome, and a hyperinflammatory syndrome marked by rapidly progressive and deadly hypercytokinemia with multiple organ failure in secondary haemophagocytic lymphohistiocytosis (sHLH) [17]. Therefore, as outlined below, current prescription cytokine modulators may be repeated as a treatment modality for reducing hypercytokinemia in COVID-19 patients.

Intriguingly, Gou et al. [18] recently recorded that host and environmental variables may potentially lead healthy individuals to irregular inflammatory reaction found in COVID-19 due to disturbance of gut microbiome characteristics. The researchers designed a blood proteomic risk score for predicting COVID-19 development to medically extreme stage and found using a machine learning model that core gut microbiota characteristics were substantially associated with proinflammatory cytokines in a group of 366 people [18]. A study found negative associations of Bacteroides genus, Clostridiales order and Streptococcus genus while positive associations of Blautia genus, Lactobacillus and Ruminococcus genus with inflammatory cytokines that were tested [18]. In addition, several possible amino acid-related pathways (such as arginine biosynthesis pathway, aminoacyl-tRNA biosynthesis pathway, and leucine, valine) that associate core microbial characteristics with host immunity among 987 participants were recorded in fecal metabolomics [18]. The central intestinal microbiological features and associated metabolites could therefore be further explored as possible predictors of human vulnerability to development of COVID-19 and intensity, which may be the ideal targets for the prevention of vulnerable individuals and the creation of treatment interventions to COVID-19 management.

4. Possible Signaling Pathways Induced by COVID-19 Disease

It is well known that viral RNAs, as pathogen-associated molecular patterns (PAMPs), are recognized by specific receptors, which involve the family of Toll-like receptors (TLRs), while the viral spike protein is bound to the host cells by the entry receptor ACE2. In particular, either the endosomal RNA receptors, TLR3 and TLR7/8, and the cytosolic RNA transmitter, the retinoic acid-inducing gene (RIG-I)/MDA5 are identified for RNA viruses such as CoVs, viral genomic RNA or intermediates during replication of virus, like dsRNA [19]. These TLRs have been repeatedly shown to stimulate multiple signaling mechanisms in human CD14+ monocytes, highly correlated with specific type IFN and cytokine release involving polarization of CD4+ T cell. As a consequence of virus identification, channels of downstream transduction, which are essential for proper antibody action such as IRF3 (IFN regulatory factor-3), signaling pathways for the nuclear factor kB (NF-kB), JAK (Janus kinase)/STAT (transcription activator and signal transducer), are enabled [20]. Identifying the most significant intracellular signaling pathways implicated in modulating host immune systems can provide valuable clues as to how to resolve the SARS-CoV-2-driven infectious disease.

Taking into consideration, particularly, the structural similarity of SARS-CoV-2 and the correspondence of pathogenic SARS-CoV infection mechanisms; it is interesting to

assume that the activation of shared intracellular pathways can be triggered by infectious viruses, particularly those that are primarily involved in the response of innate immune. It has to be shown, to date, if these sequence correlations between SARS-CoV and SARS-CoV-2 can be converted directly into related biological effects. Taking this limitation into consideration, detecting signaling mechanisms that have been changed during infectious diseases may help uncover the most important molecular clusters involved in biological mechanisms that mediate viral infections and expose main targeted molecular players. The benefit of addressing intracellular molecules instead of viral proteins is that mutations in the virus genome do not possibly counteract their effect. In addition, antiviral drugs that prevent the reproduction of viruses will choose mutational freedom, making the treatment counterproductive. Host immune response regulation thus reveals the possible benefit with viral populations of trying to exert less specific strain.

5. Conclusion

In conclusion, the two-step separation is very important: the first step of immune defense-based protection, and the second phase of damage caused by inflammation. Doctors will seek during the first step to improve immune responses, thus suppressing them in the second phase. The report can be used by clinical practitioners as it provides insights into the important mechanisms that are altered by COVID-19 virus.

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Author Contributions

The idea was conceived by YH, AY performed the critical literature review and wrote the first draft of the manuscript which was finalized by YH.

Conflict Of Interest

None to declare

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