EDITORIAL

Boosting Innate Immunity During SARS-CoV-2 Clearance

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Abstract: Currently, humanity is suffering from a highly contagious and infectious novel coronavirus disease. Due to the unavailability of any specifically approved therapy to eradicate this pathogenic virus, day by day, it is claiming more and more lives of humans. Observing the current scenario, human civilization seems to be in dangerous situation, and the development of a potential vaccine against this invisible enemy may take some more time. It was observed that the individual immune system plays an important role in the fight against the novel coronavirus. Additionally, the innate immune system of the host acts as the first line of defense against invading pathogenic viruses. The host innate immune cells can detect and detoxify the evading viruses. Thus, boosting the innate immune response via targeting activator or inhibitory immune check points pathways for enhancing T-cell immune response may potentially help the patients to fight against this deadly virus. The aim of this editorial is to discuss in brief about the pathogenesis of COVID-19, the role of innate immunity and autophagy during viral clearance.

Keywords: COVID-19, convalescent plasma therapy, innate immunity, novel coronavirus, SARS-CoV-2, pathogenesis of COVID.

1. INTRODUCTION

More than 100 years after the start of the influenza pandemic of 1918, humans now appear to be facing a new pandemic. The emergence of the recent coronavirus disease spread to every nation, causing us to suffer from this disease probably for a long period. In December 2019, Wuhan, China, some cases were reported with flu-like symptomatic pneumonia caused by a newly detected β-coronavirus [1]. World Health Organization (WHO) in January, officially named coronavirus infectious disease 2019 (COVID-19), which was mainly caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [2]. The Chinese scientist was successfully able to decode the genomic sequence of SARS-CoV-2 within a very short period span and released on 7 January 2020 [3]. This preliminary investigation boosted research on the development of therapeutic agents against SARS-CoV-2. Earlier, the world has also faced the epidemic of other coronaviruses such as in the severe acute respiratory syndrome coronavirus (SARS-CoV) at the beginning of 2003 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 [4]. These viruses are from the family of Coronaviridae, which consists of a viral genome known as +ve sense single-stranded RNA genome. Compared to other RNA viruses, this group is distinguished by considerable genetic diversity and a higher incidence of recombination that allows for easy dissemination between people and animals around the globe [5].

As a consequence, there are multiple coronaviruses within humans and animals, without triggering life-threatening illness. The genetic variation of viruses inside arbitrary intermediate hosts occasionally yields highly infectious strains that are extremely harmful to humans. The genetic and morphological identity between SARS-CoV-2 and SARS-CoV has suggested that it has its distinctive properties that led to the worldwide outbreak of this infectious pathogen [6]. As there is presently no successful cure for coronavirus diseases, considerable attempts have been made to establish vaccines and therapeutic agents. Preclinical research has demonstrated the efficacy of many countermeasures, but large-scale studies are still required. In this editorial, we have discussed in brief SARS-CoV-2 pathogenesis, the role of innate immunity and autophagy during the clearance of SARS-CoV-2 infection.

2. PATHOGENESIS OF SARS-COV-2

The structural genomic analysis of α- and β-coronavirus demonstrated that the SARS-CoV-2 genomes encode for several structural proteins: such as the glycosylated spiked (S) protein. This structural protein acts as a crucial stimulator for the human immune system with an active polybais (fur-in) breaking location at the S1–S2 boundary via 12 identified nucleotides [7]. The S protein has demonstrated an important role in viral invasion to the host via the angiotensin-
converting enzyme 2 (ACE2) receptor. The level of the viral entry to the host largely depends on the extent of the host ACE2 receptor expression and affinity of the viral S protein towards this receptor. An in-depth investigation suggested that viral invasion to the host cells triggers the production of the S protein-mediated by serine protease TMPRSS211, generated by the host cells [8]. The genetic code also encrypts several non-structural protein molecules, including RNA-dep-endent polymerase (RdRp), coronavirus primary protease (3CLpro), and papain-like protease (PLpro). SARS-CoV-2 genetic code is released into the cellular structure as a +ve sense of a single-strand RNA (ssRNA). Consequently, the SARS-CoV-2 polyprotein is generated using the patient’s cellular protein translation machinery (ribosomes) and then cleaned into target proteins via the 3CLpro and PLpro SARS-CoV-2 proteases [9]. Receptor binding domain (RBD) in the viral S protein is the highly complex component of the coronavirus genome. Further, research suggested that there are 6 RBD amino acids that play a key role in binding with the ACE2 receptors [10]. Also, it was noted that the new coronavirus has RBD that has the ability to bind with humans and other animals such as cats, rats and ferrets, having a relatively higher number of the ACE2 receptor expression [11].

3. IMMUNE RESPONSE AND SARS-COV-2 INFECTION

Clinically, newly identified coronavirus triggers a biphasic immune response. At the beginning of the infection, which includes a nonsevere incubation period, a highly selective adaptive immune response is essential to eradicate the viral infection and inhibition of infection progresses to severe stages [12]. So, methodologies to enhance immune responses (anti-sera) are definitely crucial at this point. The individual must be relatively healthy with a desirable genetic history, which provokes unique antiviral immunity for the production of an innate defensive immune reaction at the primary nonsevere incubation stage. Genetic variations in the immune response to infections are believed to lead to human differences [13]. Conversely, whenever a defensive immune response is compromised, the viral infection spreads, and significant tissue damage occurs, particularly in organs with high ACE2 expression, such as the intestines and kidneys. The impaired cells cause latent lung inflammation, which is primarily regulated by pro-inflammatory macrophages and granulocytes. At the extreme point, lung inflammation seems to be the primary cause of life-threatening pulmonary diseases. Physical fitness may be beneficial at the beginning phase of infection. During severe infection, medical intervention is essential to prevent lung injury. Efforts must be taken to reduce the inflammatory response and prevent complications [14]. Unusually, few patients return positive for the virus following discharge from the hospital, and some may even relapse. This means that it might be challenging to trigger a virus-eradicating immune response to COVID-19, at least in certain patients, and vaccinations may not be effective in such patients. Along with T/B cell responses, individuals healed from the non-severe stage must be checked for infection. Pathophysiological state of patients such as cytokine storm, level of pro-inflammatory biomarkers, immune response, etc., must be taken into consideration when assessing the vaccine’s developmental approaches. Additionally, there are many coronavirus types or subtypes. However, for vaccines specifically targeting SARS-CoV-2, it seems to be a challenging task for fast track vaccine development. Hence, consideration should be given to the Edward Jenner method of vaccine development that may reduce developmental steps and time [15, 16]. Numerous viruses affect the respiratory system and provoke various immune responses; some of them are presented in Table 1.

4. INNATE IMMUNE RESPONSES DURING SARS-COV-2 CLEARANCE

Innate immunity reflects the evolutionary conserved immune response of the host, which acts as a primary defense against infectious pathogens. These immune responses are evolutionarily conserved in the host genome, which does not deem to be prior exposure to the pathogenic antigen to be effective. This specificity and quick response differentiate innate from adaptive immunity [23]. The innate immune response depends on detecting specific pathogenic patterns through PRRs expressed on innate immune cells, which helps in the broad differentiation of infectious agents from normal human cells. The innate immune response also has demonstrated a key role in maintaining homeostasis through regulation of endogenous process that includes inflammation and cell death [24]. As evident from many studies, innate immunity has an important role in the initial identification of invading viral antigen and subsequent initiation of an adaptive immune response. The immune response related to viral infection is mediated through the involvement of numerous immune cells such as dendritic cells, macrophages, cytotoxic T cells, and Natural killer cells. Thus, it became essential to understand the dynamic interaction between innate immune cells through active in-vivo monitoring of interaction, induction, and behavior of immune cells response [25, 26]. The knowledge of antiviral immunity stimulation mechanisms will contribute to the development of novel immunotherapy, and vaccines for viral infections, inflammatory diseases and cancer [27-29]. As noted earlier, targeting those aspects of innate immune response that may potentially harm the host associated with SARS-CoV-2 may improve the pathophysiological state of patients. For example, inhibition of the Interleukins-6 receptor with tocilizumab improved the symptoms such as hypoxemia and CT opacity immediately after intervention and prevent febrile, and inflammatory storm response associated damage to the lungs [30, 31]. Convalescent plasma therapy seems to be another hope for fighting against COVID-19, till the emergence of any specific vaccine [32]. Convalescent plasma is the plasma obtained from the person successfully cured of SARS-CoV-2 infection, which contains antibodies against this deadly virus [33].
Table 1. Represents the common respiratory viruses and their immune response.

<table>
<thead>
<tr>
<th>Respiratory Viruses</th>
<th>Family</th>
<th>Primary Sign/Symptoms</th>
<th>Immune Response</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human respiratory syncytial virus (HRSV)</td>
<td>Pneumoviridae</td>
<td>Acute respiratory infections, bronchiolitis, pneumonia</td>
<td>Activation of humoral immune response and release of neutralizing serum antibodies IgG, IgA in the airways.</td>
<td>[17]</td>
</tr>
<tr>
<td>Human parainfluenza viruses (HPIV)</td>
<td>Paramyxoviridae</td>
<td>Lower respiratory infections, fever, runny nose, and cough</td>
<td>Promotion of host defense via activation of humoral immunity to both surface glycol proteins of the virus that includes hemagglutinin-neuraminidase (HN) and fusion (F). Additionally, the immune response appears with the involvement of IgG1.</td>
<td>[18]</td>
</tr>
<tr>
<td>Human rhinovirus (HRV)</td>
<td>Picornaviridae</td>
<td>Infection of lower airway epithelium, otitis media, and sinusitis</td>
<td>It involves the activation of innate and adaptive immunity for viral clearance. Viral clearance is mainly associated with the recruitment of T cells with the production of TH1 cytokines including IL-1, IL-2, IL-8, TNF-α, and IFN-γ.</td>
<td>[19]</td>
</tr>
<tr>
<td>Adenovirus (ADV)</td>
<td>Adenoviridae</td>
<td>Upper respiratory infection, bronchitis, pneumonia</td>
<td>Mucociliary clearance and coughing are the primary innate immune response during initial viral clearance. Other components of the innate immunity for viral clearance involve the release of antimicrobial peptides (e.g. cationic antimicrobial peptides), α- and β-defensins, cathelicidins, and activation of alveolar macrophages and dendritic cells.</td>
<td>[20]</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>Coronaviridae</td>
<td>Fever, cough, shortness of breath, pneumonia</td>
<td>It stimulates the production of pro-inflammatory cytokines (TNF-α, IL-6, IFN-γ and IL-12) during viral replication in macrophages and dendritic cells (DC) as part of innate immunity. Additionally, induction of both intrinsic and extrinsic apoptotic pathways occurs for viral clearance.</td>
<td>[14]</td>
</tr>
<tr>
<td>SARS-CoV</td>
<td>Coronaviridae</td>
<td>Fever, cough (initially dry), shortness of breath, diarrhea</td>
<td>Viral entry via ACE 2 receptor into the host initially triggers the defensive immune response against SARS-CoV. This virus mainly infects macrophages and T-cells. Physiological conditions with lymphopenia, thrombocytopenia, and reduced T helper (CD4+) and cytotoxic T lymphocytes (CD8+) represent the severity of the disease.</td>
<td>[14]</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Coronaviridae</td>
<td>Fever, dry cough, tiredness, shortness of breath, pneumonia</td>
<td>SARS-CoV-2 triggers a biphasic immune response. Initially, a nonsevere incubation period, in which highly selective adaptive immune response is essential for viral clearance and inhibition of the infection progresses to severe stages. The protective immune response involves the release of IgA, IgG and IgM.</td>
<td>[14]</td>
</tr>
<tr>
<td>Human metapneumovirus (HMPV)</td>
<td>Pneumoviridae</td>
<td>cough, fever, nasal congestion, shortness of breath, pneumonia</td>
<td>HMPV infection results in weak innate and aberrant adaptive immune responses represented by the activation of a Th2-type cytokine response at the preceding phase of infection, which correlates with enhanced expression of IL-10 and prolonged integration of the lung virus.</td>
<td>[21]</td>
</tr>
<tr>
<td>Human bocavirus (HBoV)</td>
<td>Parvoviridae</td>
<td>Acute respiratory tract infections, rhinorrhea, fever</td>
<td>Humoral immune response was reported against HBoV along with IgG and IgM antibodies for viral clearance.</td>
<td>[22]</td>
</tr>
</tbody>
</table>

5. AUTOPHAGY IN COMBINATION WITH INNATE IMMUNITY MAY HELP IN SARS-COV-2 CLEARANCE

Autophagy is among the three pathways used by cells for sequestration, removal, and recycling of waste; the others are proteasomal degeneration, and phagocytosis. Cells utilize autophagy to control the function of different signaling proteins [34-36], to prevent the aggregation of damaged or long-lived cells, and eradicate invading threats such as intracellular pathogenic agents [37, 38]. Autophagy has been largely related in the course of cellular responses to molecular patterns DAMPs and PAMPs with inborn immune signal pathways [39, 40]. It is reported that the autophagy mechanism is regulated through the involvement of PRRs that include TLRs, RLRS, NRLs, inflammasome, and interferon gene stimulator. This interaction includes both positive, and negative regulatory mechanisms that ensure acute inflammatory responses while suppressing hyperinflammation. Therefore, autophagy has become a vital aspect of innate immunity [41, 42]. Based on the well-understood mechanism of cross-talk between autophagy, and apoptosis, we conclude that excess-accumulation of autophagosomes triggers an apoptotic pathway that leads to apoptotic death of the infected cells and obstructs the SARS-CoV-2 replication cycle [43].
CONCLUSION

Thus, understanding of SARS-CoV-2 mediated innate immune response may begin to justify why certain viral strains lead to more severe infection and why some people become more susceptible. It is getting progressively clear that there are substantial dissimilarities in the innate immune response to a pandemic viral infection that includes, mild, moderate and severe SARS-CoV-2 infection. A thorough understanding of innate immune response related to SARS-CoV-2 may potentially help to segregate the patient with a high risk of severe COVID-19 infection [14, 15, 24, 28]. Numerous researches suggested that polymorphism in TLRs responsible for modulating immune responses to infectious pathogens. Polymorphisms of the TLRs associated with viral illness are likely to influence the immune response to SARS-CoV-2. Similarly, genetic variation of the host may be responsible for a different level of defense against viral infection. Additionally, various groups of people having compromised immunity with chronic diseases such as cancer, kidney disease and chronic obstructive pulmonary disease are more susceptible to SARS-CoV-2. The important outcome of identifying susceptibility factors to SARS-CoV-2 may help in segregating subjects with the urgency of therapeutic intervention or need for prophylaxis [44-46].

LIST OF ABBREVIATIONS

SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus-2
MERS-CoV = Middle East Respiratory Syndrome Coronavirus
SARS-CoV = Severe Acute Respiratory Syndrome Coronavirus
COVID-19 = Coronavirus Infectious Disease 2019
ACE-2 = Angiotensin-converting Enzyme 2
RBD = Receptor Binding Domain
DAMPs = Damage-associated Molecular Patterns
PAMPs = Pathogen-associated Molecular Pattern
PRRs = Pattern Recognition Receptors
TLRs = Toll-like Receptor
RLRS = Retinoic acid-inducible Gene-I-like Receptors
NRLs = Nucleotide-binding Oligomerization Domain (NOD)-like Receptors
CT = Computed Tomography

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

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http://dx.doi.org/10.1038/s41586-018-0657-2 PMID: 30356220


http://dx.doi.org/10.1016/j.toxlet.2020.02.013 PMID: 32112876


http://dx.doi.org/10.1038/ni.3157 PMID: 25988887


http://dx.doi.org/10.1016/j.autrev.2020.102568 PMID: 32376398


http://dx.doi.org/10.1111/sij.12771 PMID: 31054156


http://dx.doi.org/10.10111/j.vjht.12980 PMID: 30128622


http://dx.doi.org/10.4444/swm.2020.20246 PMID: 32277836