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Review Article

Ongoing COVID-19 Pandemics by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the Host Protective Immunity Response: A Simple Outline

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Abstract

Starting from the last of December to date, the pandemic onset of acute respiratory syndrome coronavirus 2 (SARS-CoV2) causing the COVID-19 (corona virus disease 2019) throughout the world appears extremely fatal on the aspect of public health with the highest rate of mortality amongst all disease outbreaks within the last hundred years. In the meantime, lots of novel works to unravel the protective mechanisms against this viral attack have been conducted; and even the specific antiviral vaccine has undergone the trial. The molecular mechanisms underlying the viral epidemiology have been well documented. Aside to lots of reports consisting of the in depth knowledge about the genetics, pathogenesis, the antibody-enhanced viral entry; the host immunity escaping strategies of the respiratory viruses as well the SARS-CoV2, the present review summed up the major molecular and immunological issues, especially the escaping means of the host innate immunity related to COVID-19 briefly and simply as an incremental knowledge for the public awareness.

Keywords: *COVID-19; Epidemiology; Innate Immunity; Public Health*

Introduction

The 2019-nCoV coronavirus, belonging to the coronavirus (CoV) family (single-stranded RNA viruses), triggering the atypical pneumonia, has already emerged as the cause of respiratory illness apparently originating in Wuhan, the largest metropolitan area in China's Hubei province, basically from a seafood wholesale market [1-3]. However, although visits to the market have been linked to the initial COVID-19 outbreak; it should be noted (according to WHO) that there were earlier cases that are unrelated to this market in China; and actually still it's not that clear where the virus emerged from [4]. After the H_1N_1 (2009), polio (2014), Ebola in West Africa (2014), Zika (2016) and Ebola in the Democratic Republic of Congo (2019), the COVID-19 outbreak is the sixth public health emergency of international concern. The study of etiology of the illness (the emerging respiratory disease outbreaks) caused by the newly discovered virus (i.e. the 2019-nCoV coronavirus or the COVID-19) was first initiated by the Chinese Center for Disease Control and Prevention (CDC) [5]. It is to be pondered that the 2019-nCoV has been termed as the SARS-CoV-2 virus by the task of experts of the International Committee on Taxonomy of Viruses (ICTV) [5]. It's spread towards the subcontinental countries, the European countries and in the US is a dreadful clinical alarm. As of 25 April 2020, data from the World Health Organization (WHO) have shown that approximately 2700000 confirmed cases have been identified in more than 200 countries, with nearly 182000 death cases [6].

Indeed, the history of the last twenty years unraveled the onset of acute respiratory syndrome coronavirus (SARS-CoV, a novel betacoronavirus) epidemics; and it is to be pointed that the Middle East respiratory syndrome coronavirus (MERS-CoV) was first

recognized in Saudi Arabia in 2012 [4,5]. SARS-CoV incited a massive epidemic outbreak with two dozen countries including China. It is stipulated from the phylogenetic study that the SARS-CoV have originated from bats and then transmitting into other mammalian hosts before infecting humans [7]. Besides the zoonotic transmission, the most frequent reason of infection appears to be the human-to-human transmission mode [2]. One interesting finding has been made that the children can be less affected by the COVID-19 like the SARS-CoV [2]. The recent extensive modeling of the epidemic curve of the virus (estimating the basic reproduction number) of 2019-nCoV within a two weeks' frame (January 10 - 24, 2020) in China revealed the exponential attribute of the early outbreak, which in turn projected the viral transmissibility rate as well although the dynamics of SARS-Cov-2 are still unknown [3]. However, the use of in silico docking to know about the COVID-19 spike-receptor binding is in progress which may aid in therapeutic development of the infected cases [2]. Structural analysis of the virus pointed out an important facet of infection whereby it was speculated that the virus particle might bind to the angiotensin-converting enzyme 2 receptor in humans which in turn, might render the infected patient prone to the respiratory complications [7,8]. The very recent comparative bioinformatics analysis on the viral genome collected from an infected patient has been done too [1,3].

Bestowed with the "very high" level alert for the COVID-19 epidemics announced by the World Health Organization (WHO), other health organizations round the globe as well as the relevant scientists are working to mitigate the viral infection principally focusing on the prevention and therapeutic strategies through the study of clinical continuum of the ongoing disease, the viral transmission mechanisms and inventing the new and rapid diagnostics. As a consequence, the travel-related infection cases have been well documented so far [1,9]. Interestingly, a novel molecular mechanism for antibody-enhanced viral entry has been unraveled which is expected to impart contribution on possible vaccination and antiviral therapies [10]. Moreover, scientists are not only trying to develop vaccine against COVID-19 but also they are in a momentum to resolve a puzzle about the effectiveness of the vaccines targeted for SARS-CoV or MERS-CoV against the COVID-19 [1].

Despite a lot of significant works have been performed and the wealth of significant molecular insights have been noted within a very short period of the beginning of the COVID-19 pandemics, current review simply summarized the major issues which may be easily communicable to the general people for their easy understanding about the virus. Moreover, obtaining a complete understanding of the interface between Coronaviruses and the host innate immune systems may aid to the knowledge on the viral persistence especially along the lung which in turn would be useful to decrease the threat of lung inflammation triggered by the virus. The information on the host innate immunity evasive strategies are further linked to the development of vaccines as has been revealed from various reports [1,7]. Thus, the present review simply correlated the viral genome towards its epidemiological traits and the evasion strategies from the host immune cells.

Genomic features in correlation with COVID-19 infection symptoms and epidemiology

Gene annotation and genome sequencing of virus is certainly an important tool for the complete understanding of the viral infectivity and the epidemiological studies. COVID-19 is an RNA virus consisting of 26 to 32 kb genome which has been well reported to impart some interesting tricks for evading the host mediated immune response as will be discussed later [11]. The predicted coding regions of 2019-nCoV showed the presence of a longer spike protein in the envelope comparable with the SARS-CoV and MERS-CoV [1,7]. The spike protein is known to conduct the receptor binding as well as the membrane fusion which is important for the viral propagation [10,12]. The phylogenetic analysis by the same group exhibited the gene encoding the RNA-dependent RNA polymerase in COVID-19, making it a novel beta-coronavirus. Since the COVID-19 is an RNA virus, the possible evolutionary rate may be expected to be 10^{-4} base substitutions per site per year, with the concomitant mutations at every replication cycle [5,13]. Moreover, based on sequence similarity, it has been suggested that COVID-19 originated from a single source within a very short time; and therefore the possible mutations are not unlikely [7]. Besides, the antibody-dependent enhancement (ADE) of viral entry has been reported to be associated with the epidemiology as well

as for the development of the appropriate vaccine; and even for the motto of antibody-based drug therapy [10]. However, it is worth to note that the innate immune evasion strategies is the major cause of the COVID-19 pathogenesis as described later [11].

The spread of the COVID-19 is principally mediated by human-to-human transmission via droplets or direct contact [8]. The viral infection (termed as novel coronavirus pneumonia or Wuhan pneumonia) develops within 7 days on an average, with the onset of headache, fever, sore throat, cough, upper airway congestion, pharyngalgia, myalgia and diarrhoea [8]. Pleural effusion or lymphadenopathy in the chest can also be noticed [14]. Within the adults, the cardiovascular diseases and hypertension followed by diabetes mellitus were the most common underlying diseases [8]. It is to be noted that the sequential secondary bacterial infections are not surprising during the viral infections.

Demolition of Innate immunity

The lung tissue along with the respiratory tract is constantly exposed to microorganisms inhaled from the air which is actually counteracted by the mucus layer; i.e. the first line of defense of the innate immune system at the nasopharynx up to the alveolar membrane [15]. A set of cellular innate immune sensors are supposed to recognize the bacteria and viruses (common viruses invading the lungs like the coronaviruses, rhinoviruses, influenza viruses, etc.) upon their entry along the respiratory tract, followed by the subsequent downstream signaling of the protective immune cells including the alveolar macrophages, the airway epithelial cells, innate lymphoid cells (the innate lymphocytes), neutrophils and dendritic cells to establish a sort of antiviral state in the lungs [11]. In course of respiratory tract infections, when these cells are completely functional, the innate immune response signaling cascade is known to be triggered with the recognition of pathogen-associated molecular patterns (PAMPs) by the pattern recognition receptors (PRRs). Specifically, for the RNA viruses invading the lungs, the toll-like receptors (TLRs) 3, 7 and 8 are expressed [11].

How does COVID-19 escape the host innate immunity?

Eventually, suppression of such intracellular innate antiviral responses will cause the viral infection. Like the rhinoviruses, the COVID-19 positive stranded RNA has been shown to encode at least 2 proteases possessing the capacity of cleaving the cells of the innate immunity. Coronaviruses have been reported to use a blend of approaches to accomplish the "host shut-off" in course of transcription and translation by means of Nsp1 protein, the 5′-terminal subunit of the replicate polyprotein of the virus [11] was shown to cause host shut-off by binding to cellular factors of the translation machinery thereby preventing translation of host mRNAs. Surprisingly the viruses consisting of positive single stranded (+ss) RNA genome (i.e. COVID-19 and rhinoviruses invading the lungs) may replicate utterly in the cytoplasm by modifying the intracellular membranes to form specific replication organelles which is predictive of protecting the recognition of viral RNA by the innate immune sensors [16]. The formation of such membranous replication organelles for viral the RNA has been already anticipated as a major line of attack the host by the respiratory viruses as well as to circumvent the recognition by the host innate immune cells [11]. The viral endoribonuclease activity (in one of non-structural proteins of COVID-19) is an important means of avoiding the innate immunity [17]. Another predictive as well as exciting strategy of escaping the host immunity underlies the mechanism of the 5′ terminus of the viral RNAs whereby the viruses directly modify their RNAs (possibly without using the host machineries required for post transcriptional modification) to stay away from the detection by the foreign RNA sensors employed by the innate immune cells of the host [11,18]. Such a tricky mechanism permits the viral mRNAs to be further recognized by the host translation machinery which ensures the synthesis of new viral particles.

Cell mediated/adaptive immunity

For combating the respiratory viruses, several immune cells including the natural killer (NK) T cells, mucosal-associated invariant T cells, and neutrophils are thought to form a network between the innate and adaptive mechanisms [11]. The immunological memory, usually associated with the adaptive immune system, may also play a role in the innate immune response against the respiratory viruses

[19]. Such epigenetic changes on the innate immune factor genes in the specialized immune cells (like macrophages) are triggered upon activation of the innate immune response which positively influences the response on subsequent viral encounter (with the possible aid by the $CD8^+$ T cells and the interferon-gamma; i.e. IFN-g); thereby eliciting an adaptive immune response [20]. A neutralizing monoclonal antibody (MAb) was found to target the receptor-binding domain (RBD) of MERS-CoV spike, permitting the viral entry. MAb has also been noticed to bind to the cell surface of the immunoglobulin G (IgG) Fc receptor which was predictive of directing the viral entry through a cascade of pathways [10]. It is to be noted that because of the remarkably elevated neutralization activity, the neutralizing mAbs has already been proposed as the promising candidate therapeutics against MERS-CoV infection [21]. Similar strategy could be useful for the COVID-19; however, extensive research is still required to chalk that out.

Possible treatment strategies

In order to treat the infection by the COVID-19, certain antiviral agents like oseltamivir, ganciclovir and lopinavir/ritonavir tablets have been used in case of few patients though so far no effective mitigating drug has been found [8,22]. However, the usage of the nucleoside analogues, neuraminidase inhibitors, remdesivir, umifenovir, DNA synthesis inhibitors, and chloroquine (posing the *in vitro* effects on hindering the post-translational modifications of newly synthesised proteins of viruses; i.e. inhibition of glycosylation), angiotensin-converting enzyme 2-based peptide and a novel vinylsulfone protease inhibitor is under consideration [8,23,24]. People should avoid close contact with the persons with acute respiratory infections; they should maintain the practice of frequent hand-washing; patients with symptoms of acute respiratory infection should use cough etiquette; i.e. to maintain enough distance and to use disposable tissues or clothing during coughing or sneezing [25]. It's to be pondered that all possible efforts are being made to reduce the global proliferation of the viral particle including the betterment of the healthcare systems, increasing the public health awareness and hygiene, adhering to the COVID-19 public-health recommendations, and to promote the in time diagnosis of the virus as well as the possible treatments including the development of appropriate vaccines.

Conclusion

The pandemic outbreak of COVID-19 is surely the most dreadful clinical threat so far in this century triggering the immense rate of death around the world. Only within the three months of the onset of this virus, several unfathomable researches have been conducted and published for the awareness and propagating the knowledge to the relevant health professionals. Current review simply summarized the major issues related to COVID-19 which may be easily understandable towards the general community. The scientific knowledge based on the viral genome and epidemiology; and especially the evasion strategies of the host immune system by the virus discussed in this review may boost the local physicians and paramedics to fight against the virus. The general people may also be benefited by gaining the information noted here in a comparatively uncomplicated way. However, the effectual choice of antiviral therapy and vaccination are still quite obscure which demand the public health authorities (the local legislative bodies) to keep monitoring such pandemic situation. One important thing is to be confirmed that the real data or the critical updates about the spread of this Novel Coronavirus should be brought up publicly so that they can be aware and rationalized about the fatality and the morbidity of the COVID-19 infection.

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