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AN UPDATE ON THE NOVEL CORONAVIRUS: SEVERE ACUTE RESPIRATORY SYNDROME- CORONAVIRUS- 2

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ABSTRACT The recent Coronavirus disease-19 (COVID-19) pandemic caused by novel severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has put the world under the burden of a public health emergency of international attention with China, Italy, United States, Spain and Germany being the most affected. While WHO has recommended isolation of confirmed and suspected cases around the world to combat the increasing transmission of the virus and the clinical management has its focus on reducing the clinical symptoms and supportive care, scientific community is trying hard to develop an effective treatment strategy against SARS-CoV-2 by targeting the spike glycoprotein which is the main cause of antibody neutralization. This review focuses on the epidemiology, antigen presentation, pathogenesis, management and treatment strategies related to SARS-CoV-2.

KEYWORDS : Coronavirus, SARS-CoV-2, symptoms, treatment strategies

INTRODUCTION

The initial twenty-seven cases that were detected in the Wuhan City of China were all found to have connection with the Huanan Seafood Wholesale Market (29). However, the initial batch of the confirmed cases of COVID-19 was neither exposed nor even had any relation to Huanan Wholesale Market. This confirmed that this spread is due to the transmission among humans. Later, the Chinese health authorities after investigation declared that a novel coronavirus was the reason for this outbreak in the city of Wuhan (21).

Coronaviruses are the virus that causes disease in humans and in certain species of animal like cattle and camels (22). Although animal to human transmission of coronavirus is rare, this new identified strain is assumed to be from bats, although according to one study pangolins could also be the origin (18).

This new novel strain of coronavirus was detected in December 2019, and became global concern in January 2019, when its spread fastens to an alarming number of people. “Coronavirus as a significant threat to the world” statement was given by World Health Organization, and was finally declared as global health emergence on 30 January 2020. The responsible virus was named as SARS-CoV-2 by the International Committee on Taxonomy of Viruses. According to WHO, it was important to give an official name to the virus which would neither refer to a particular individual or group of people or animals or geographical location, considering which the WHO named Coronavirus disease as COVID-19 on 11 February 2020. 'CO' in COVID-19 stands for Coronavirus; 'VI' for virus, 'D' for disease and 19 is the year of detection i.e. 2019. This name would also help WHO to use the standard format in case of any future outbreak of Coronavirus (16).

COVID-19 EPIDEMIOLOGY

With the rapid spreading of COVID-19 in Wuhan followed by other parts of China, several cases were soon detected in many other countries throughout the globe including Asia, Australia, Europe, Africa and the America. On 20 January 2020, China officially confirmed 200 cases infected with COVID-19 (6). Meanwhile, on 25th Feb 2020, Chinese scientists sequenced the genome of COVID-19 as reported in Asian Scientist Magazine (3). Table 1 shows the comparison of COVID-19 cases with the previous coronaviruses: SARS-CoV and MERS-CoV.

TABLE-1 COMPARISON-COVID-19, SARS-CoV & MERS-CoV

Virus	Year/Date	Total Cases	Total Deaths
SARS-CoV	2003	8,273	775 (13)
MERS-CoV	2013	1,139	431 (13)
SARS-CoV-2	As on 27th Feb,2020	82,623	2,858 (13)
SARS-CoV-2	As on 5th Apr, 2020	1 133 758	62,784 (1)

Total mortality rate of COVID-19 is estimated at 3.46% as per the published data from Chinese Center for Disease Control and Prevention (China CDC). The outbreak of COVID-19 spread nationwide and across nations in a short span of time (27).

In Italy, the very first coronavirus case was confirmed on 31 January 2020. Batch of 16 cases were later confirmed in Lombardy on 21st February 2020 and the very next day 22nd February confirmed the first death in Italy along with additional 60 new cases. Moreover, the case of COVID-19 appeared from all over Italy. On March 6th, 2020 the Italian College of Analgesia, Resuscitation and Intensive Care (SIAARTI) published medical ethics recommendations in order to determine the priority of patient's treatment on the basis of severity of condition. At present, as of 26th March 2020, Italy is among world's centre's of active COVID-19 cases with 62,013 active cases. There are total of 80,589 confirmed cases, with 8,215 deaths (13). Moreover, on 19th March 2020, Italy was considered as highest number of confirmed deaths throughout the globe (17).

At present, COVID-19 cases are rising quickly in USA and Italy followed by the entire world, which is posing a big burden to public health. As of March 24th, 2020, there are more than 392,000 cases of COVID-19 reported in nearly 190 countries and territories (9, 28).

PATHOGENESIS AND VIROLOGY OF SARS-COV-2

Symptoms associated with COVID-19

Before the COVID-19 pandemic occurred, there were six known CoVs that caused respiratory diseases in the humans; the more severe SARS-CoV, MERS-CoV, and mildy severe HCoV-229E, HCoV-OC43, HCoV-NL63, HKU1 (8).

The outbreak of the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which exhibited phylogenetic similarity to SARS-CoV, causes COVID-19 disease. After analysing the cases, it was inferred by the scientists that COVID-19 infection emerges after an incubation period of about 5.2 days. The period between onset of symptoms and death ranges from 6 to 41 days and this time period is governed by the patient's age and his immune system. Transmission among humans occurs primarily via direct contact or droplets spread by coughing or sneezing from an infected person (15, 25).

The significant symptoms of COVID-19 are fever, cough, sneezing, tiredness, production of sputum, headache, dyspnoea, lymphopenia, hemoptysis and gastrointestinal symptoms like diarrhoea. The chest CT scan reported pneumonia and other features like RNAaemia (serum SARS-CoV-2 viral load), acute respiratory distress syndrome (ARDS), cardiac injury and grand-glass opacities that subsequently led to increased mortality. Chest radiographs also showed an infiltration in the upper lobe of the lung which linked the disease with dyspnea and hypoxemia (23).

Cytokine storm associated with COVID-19

Blood tests of COVID-19 patients showed high levels of cytokines and chemokines which included IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. The severely affected patients of COVID-19 monitored in the intensive care unit were reported to have elevated levels of pro-inflammatory cytokines which included IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα. These pro- inflammatory cytokines have been reported to be the factors for promoting the severity of this disease (23). This increased cytokine production leads to an aggressive attack to the body by the immune system, hence leading to ARDS and multiple organ failure. Eventually, death can occur in more severe cases as it happened in case of SARS-CoV and MERS-CoV infections (5).

Analysis of genomic characteristics of SARS-CoV-2

Coronaviruses belong to the family *Coronaviridae* that replicate in the cytoplasm of the host cell (8, 19). It is an enveloped positive strand RNA virus with largest known RNA genomes of 30-32 kb (24). The SARS-CoV-2 genome has similarity to other CoVs consisting of minimum ten open reading frames (ORFs) (5). The rates of mutation of RNA viruses is greater when compared to the DNA viruses which propounds that CoVs have a more effective adaptation process for their survival. The ORFs present in one-third of the CoV genome codes majorly for four different proteins that are the integral part of the viral structure (5, 24). The spike glycoprotein (S) which binds to the host cell receptor and helps in facilitating the entry of virus in the host cell, envelope protein (E) which is responsible for interacting with the membrane protein for formation of the viral envelope, membrane protein (M) which is the primary organiser of the CoV assembly and determinant of the viral shape, and the nucleocapsid protein (N) which is bound to the RNA genome. The nucleocapsid protein makes a complex with the RNA genome and makes an arrangement of helical capsid which is found in the viral envelope. The S protein possesses the site of viral attachment to the host cell. Small spikes of hemagglutinin esterase (HE) proteins on the membrane are present in some coronavirus virions. The transmembrane proteins, M and E are also involved in assembly of the virus (8).

The virus releases its RNA genome into the host cell after gaining entry into the host cell. It then translates its genome into two polyproteins and the structural proteins which leads to the replication of the viral genome (5). Figure 1 illustrates the structure of coronavirus and its structural proteins (5, 14).

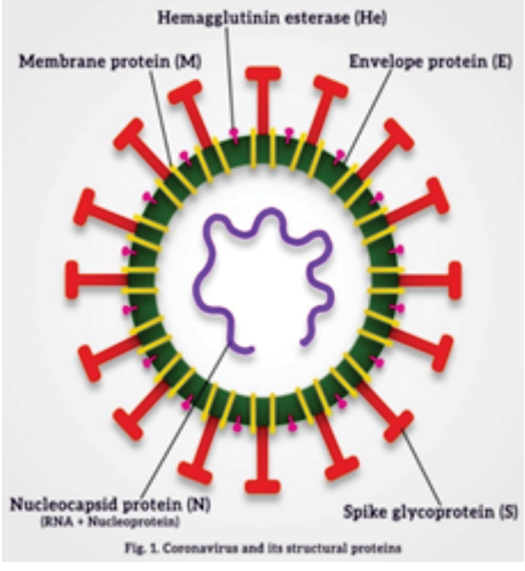

Fig. 1. Coronavirus and its structural proteins

Viral infection is associated with ACE2 receptors

The viral infection initiates with the binding of the virus to the host cell receptors via the ACE2 receptor present on the host cell and the virus then fuses with the cell membrane to gain entry into the host cell. Evidences suggest that the primary target of this virus is the lung epithelial cells and hence, transmission of SARS-CoV among humans is facilitated by the association of the receptor-binding domain of the viral spikes (which has sequence similarity to that of the COVID-19 spikes), to the host cell receptor, angiotensin-converting enzyme 2 (ACE2) receptor (5,7).

Antigen presentation by HLA and role of polymorphisms

There is not any report suggesting about the pathogenesis of SARS-CoV-2, however, the previous work on SARS-CoV and MERS-CoV can help us understand and infer about the mechanism of COVID-19 pathogenesis for directing towards viral immunity via the antigen presenting cells (APC) as it gains entry into the host cell. The antigenic peptides presented by the major histocompatibility complexes (MHCs) or Human leukocyte antigen (HLA); particularly MHC I molecules, are recognised by the virus specific cytotoxic T lymphocytes (CTLs). Studies suggest that HLA polymorphisms such as HLA-B 4601, HLA-B 0703, HLA-DR B1 1202 and HLA-Cw 0801 show an increased susceptibility towards CoV infection. (5, 7). On the other hand, HLA-DR0301, HLA-Cw1502 and HLA-A 0201 alleles are linked to the resistance from SARS infection (5). Other than the HLA polymorphisms, the polymorphisms of mannose-binding lectin have also been linked with the antigen presentation and risk of SARS-CoV infection (5).

Immune evasion by the SARS-CoV-2

Pathogen- associated molecular patterns (PAMPs) present on the pathogen can be recognized by the pattern recognition receptors (PRRs) of the host cell to elicit an immune response. However, the SARS-CoV and MERS-CoV can escape the host immune responses by enhanced production of PRR lacking double-membrane vesicles. Moreover, they replicate in these vesicles and their dsRNA remains undetected by the host. Protective effects of IFN-I (IFN-α and IFN-β) have been reported on SARS-CoV and MERS-CoV infection, however, the protein 4a of MERS-CoV blocks its induction. Coronavirus can also affect the antigen presentation by downregulating the gene expression specific to it (20). This suggests that the drug development strategies must focus on overcoming the immune evasion of SARS-CoV-2.

THE IMMEDIATE ANCESTOR CONFUSION

The immediate ancestor of SARS-CoV 2 is yet to be investigated, however, some studies report that SARS-CoV-2 share 96.2% overall genome sequence similarity with the bat coronavirus RaTG13 found in *Rhinolophus affinis* from Yunnan Province. However, this bat coronavirus does not use the same ACE2 receptor as SARS-CoV-2 does. Secondly, betacoronaviruses which were found in the endangered species of small mammals known as pangolins (consumptions as source of meat in Southern China) showed 90% overall nucleotide sequence identity but due to divergence in the sequence over the whole genome, it cannot be stated as the immediate ancestor (30). It has been reported that it is likely that SARS-CoV originated in bats and eventually adapted to the non-bat ACE-2 variants and gradually crossed the species to cause infection in humans (5, 14).

TREATMENT AND MANAGEMENT

COVID-19 Management

COVID-19 is considered as community transmitted disease occurring through lung related small drops released during coughing and sneezing (2, 3, 4). Mostly spread either when people are closer to one another or when people touch contaminated area and then their face. The common symptoms of COVID-19 include fever, coughing, cold and shortness of breath. Complications such as pneumonia and acute respiratory distress syndrome have also been linked to COVID-19. Currently, no vaccine or particular antiviral medicine is available or established for COVID-19 (3). Majority of the treatment strategies being adopted by the medical practitioners for managing COVID-19 rely on past experiences of SARS- and MERS- CoV infections.

WHO recommends supportive care that includes oxygen therapy, fluid therapy and antibiotics for treatment of secondary bacterial infections. The suspected or confirmed patients of COVID-19 are isolated to prevent the transmission. The efficacy of remdesivir, lopinavir/ ritonavir alone or in combination of interferon- β has been reported. However, the clinical trials and safety index needs to be analysed before concluding them effective in humans as effective in managing COVID-19 (11).

Potential COVID-19 drug development strategies

Some of the potential sites of coronavirus can be targeted for developing new drugs. For instance, protease inhibitors could be used to prevent RNA polymerase processing or can disintegrate Viral S glycoprotein. As in case of influenza viruses A and B, neuraminidase inhibitors inhibit viral replication, similarly, viral replication can be

limited with the help of coronavirus acetylesterase inhibitors (22).

Furthermore, viral entry can be blocked by the inhibitors that inhibit membrane fusion, as encountered against the human immunodeficiency virus. Vaccines are available for coronaviruses that infect animals, however for humans; no vaccine has been formed yet. Construction of vaccines with wild type coronaviruses could pose a risk, therefore, killed or subunit vaccines that constitute spike glycoproteins along with other polyproteins might help in impeding the lower respiratory tract diseases in humans (29).

Studies on experimental animals have reported some casesin which some vaccines against animal coronaviruses which involved wild type virus had resulted in increased the disease severity. There is a possibility that the current outbreak can be controlled and the virus elucidated by quarantine. However, there is an urgent need to develop safe, effective and reliable drugs and vaccine against COVID-19.

Challenges to treatment strategies

The major target for CoV drugs and vaccines is the spike glycoprotein (S) which is the primary inducer of antibody neutralization. Till date, the attempts to develop effective vaccines against human CoV infection such that MERS and SARS have not been fruitful and hence, the scientific community has not been able to develop any licensed antiviral treatment or vaccine for these infections (3).

One of the most important factors for antiviral drug development is the demand in the market which lasts only for the period while the outbreak lasts (4). The issue with antiviral drugs is that when it is ready, there are no patients for clinical trials. Due to this issue, the pharmaceutical companies lack interest (3).

The mouse does not show interaction with MERS or SARS viruses due to the differences in the ACE2 receptors, hence the mouse needs to be engineered first to delete the mouse ACE2 and acquire the human ACE2 in place of that (4).

CONCLUSION AND FUTURE PROSPECTS

There have been a number of theories for the spread of this virus from China. While it is believed that this virus might have transmitted to the humans via bats, some claim that it might have deliberately escaped from a research centre. SARS-CoV-2 has shown sequence similarity to the previous CoVs, particularly SARS-CoV and MERS-CoV. The early death cases of COVID-19 involved older persons and weak immunity has been the possible reason for a fast progression of COVID-19. Further research needs to be done to know about the potential transmission modes, virus adaptation and evolution mechanisms. Spike glycoprotein has been targeted for developing drugs against the virus and suitable animal models for SARS-CoV-2 infection needs to be build for analyzing the replication, transmission and pathogenesis of the virus. With help of the existing information and drug development strategies related to previous MERS and SARS, further research for gaining more knowledge and information about the new CoV needs to be done in order to be able to curb the present pandemic to save lives and to be able to combat any future outbreaks.

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