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Molecular Structure, Pathogenesis and Virology of SARS-CoV-2: A Review

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Abstract

SARS-CoV-2 or 2019 n-CoV is a newly identified coronavirus which has a high similarity with SARS CoV. The emergence of SARS-CoV-2 has resulted about 1850220 cases and 114215 deaths worldwide up to 13th April, 2020. The clinical criteria of SARS-CoV-2 pneumonia range from mild to critically ill cases. To characterize and control the disease, Chinese authorities did an immediate investigation, including isolation of suspected people, close monitoring of contacts, epidemiological and clinical data collection from patients, and development of diagnostic and treatment procedures. SARS-CoV-2 poses a significant public health risk for human transmission via the S protein–ACE2 binding pathway. It's spike (S) glyco protein promotes entry into cells. To date, the SARS-CoV-2 genome has been considered genetically more stable than other pandemic viruses like SARS-CoV or MERS-CoV. The rapid global spread of 2019-nCoV, which prompted the PHEIC declaration by WHO, signals the urgent need for corona virus vaccines and therapeutics. [*Bangladesh Journal of Infectious Diseases, April 2020;7(suppl_1):S36-S40*]

Keywords: SARS-CoV-2; 2019n-Co-V; COVID-19; MERS-CoV; RBD; ORF; molecular structure; virology; pathogenesis

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Introduction

The major outbreak of human fatal pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is a newly documented illness that has spread fast throughout Wuhan (Hubei province) to other provinces in China and around the world since the beginning of the 21st century[1,2].

Severe acute respiratory syndrome (SARS) outbreak occurred in Between November 2002 and July 2003 (9.6% fatality rate), with the majority of cases in mainland China and Hong Kong. It was a viral respiratory disease caused by the SARS

coronavirus (SARS-CoV)[3]. Another corona virus which was first detected in Saudi Arabia in 2012 named Middle East Respiratory Syndrome Coronavirus (MERS-CoV) with a fatality rate of 35% cases.

Both SARS-CoV and MERS-CoV are zoonotic viruses and bat/civet and dromedary are their hosts respectively. No specific therapeutic drug or vaccine has been approved for the treatment of human coronavirus still date. Therefore, CoVs are considered to be a kind of viruses, of which the outbreak poses a huge threat to humans. Because SARS-CoV-2 cases were discovered at the end of 2019, this coronavirus was named as 2019 novel coronavirus or "2019-nCoV" by the World Health Organization (WHO) on January 12, 2020. 2019-nCoV is highly homologous with SARS-CoV. So the International Virus Classification Commission (ICTV) classified 2019-nCoV as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on February 11, 2020. At the same time, WHO named the disease caused by 2019-nCoV as COVID-19[2,4].

As of 13 April 2020, the total number of patients has risen sharply to 559409 in USA, 166831 in Spain, 156363 in Italy and total 1850220 cases in the whole world. But 430455 patients have already recovered. The case fatality rate was estimated to be 4 percent in China, but varies significantly between countries[4].

Coronaviruses

Coronaviruses have been identified in several avian hosts, as well as in various mammals, including camels, bats, masked palm civets, mice, dogs, and cats[5]. In humans, coronaviruses mostly causes mild respiratory tract infections such as some cases of the common cold, and others that can be lethal, such as SARS, MERS, and COVID-19[6,7]. Coronaviruses are often classified into four genera: Alpha, Beta, Gamma and Delta coronavirus. Alpha coronaviruses include Human coronavirus 229E, Human coronavirus NL63, Miniopterus bat coronavirus 1, Miniopterus bat coronavirus HKU8, Porcine epidemic diarrhea virus, Rhinolophus bat coronavirus HKU2, Scotophilus bat coronavirus 512, while the beta coronaviruses include Beta coronavirus 1, Human coronavirus HKU1, Murine coronavirus, Pipistrellus bat coronavirus HKU5, Rousettus bat coronavirus HKU9, Severe acute respiratory syndrome-related coronavirus/SARS-CoV, Severe acute respiratory syndrome coronavirus 2, Tylonycteris bat coronavirus HKU4, Middle East respiratory syndrome-related coronavirus/ MERS-CoV, Human coronavirus OC43, Hedgehog coronavirus 1 (EriCoV).Gamma coronavirus includes Beluga whale coronavirus SW1, Infectious bronchitis virus and lastly Delta coronavirus includes Bulbul coronavirus HKU11 and Porcine coronavirus HKU15[7]. The average evolutionary rate for coronaviruses is roughly 10^{-4} nucleotide substitutions per site per year, as it is a typical RNA virus, 1 with mutations arising during every replication cycle[5].

Origin of SARS-COV-2

Many of the early cases were linked to Huanan seafood Wholesale market in Wuhan city, Hubei province, where the virus is thought to have originated[8,9]. Genetic analysis has revealed that it shares the highest level of genetic similarity (96.3%) with CoV RaTG13.The WHO considers bats the most likely natural reservoir of SARS-CoV-2, but differences between the bat coronavirus and SARS-CoV-2 suggest that humans were infected via an intermediate host[4]. Bats acted as the natural reservoir in both SARS-CoV and MERS-CoV, and masked palm civet for SARS-CoV and dromedary camels for MERS-CoV acting as an intermediate host, with humans as terminal hosts. Therefore, on the basis of these, it seems likely that the 2019-nCoV causing the Wuhan outbreak might also be initially hosted by bats, and might have been transmitted to humans via currently unknown wild animal(s) sold at the Huanan seafood market[5]. Recently, CoV sequences closely related to SARS-CoV-2 were obtained from confiscated Malaya pangolins in two separate studies. Pangolin SARS-like CoVs (Pan_SL-CoV) form two distinct clades corresponding to their collection location. Pan_SL-CoV_GD from Guangdong (GD) province in China and are genetically more similar to SARS-CoV-2 (91.2%) than Pan_SL-CoV_GX from Guangxi (GX) province (85.4%)[11]. The receptor-binding domain of the S protein of the newly discovered Pangolin-CoV is virtually identical to that of 2019-nCoV, with one amino acid difference[12]. No other mammals other than bats documented to be infected by a 2019-nCoV related coronavirus till date except Pangolin. It is remarkable that two distinct clades of CoVs are found in pangolins and that both are also related to 2019-nCoV. This suggests that these animals may be long-term reservoir hosts for these viruses, which is surprising as pangolins are solitary animals with relatively small population sizes[8]. Extensive recombination among bat coronaviruses and strong purifying selection pressure among viruses from humans, bats and pangolin may allow jumping between new hosts[11].

Structural Biology of SARS COV2

SARS-CoV-2 is known to be an enveloped virus. It is a positive sense single stranded RNA (+ss RNA) virus. It's RNA sequence is approximately 30,000 bases in length[4]. As SARS-CoV-2 incorporates a polybasic cleavage site which is characteristic known to increase pathogenicity and transmissibility in other viruses, it is unique among known beta-coronaviruses. The virion is approximately 120 nanometres in diameter[13,14]. The helical nucleocapsid surrounded by a host-derived lipid bilayer and genome is packaged into it[15]. The relatively large size and lipid envelope makes it highly susceptible to steps with virus inactivation and removal capacity used during the manufacturing processes, such as solvent-detergent (S/D), low pH incubation, caprylate, pasteurization or dry-heat treatments, nano-filtration or fractionation processes and others. The effectiveness of these processes has been demonstrated on other lipid-enveloped model viruses which are quite similar to 2019-nCoV, like human coronavirus 229E and OC43, SARS-CoV and porcine corona virus TGEV[16]. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins; the N protein holds the RNA genome, and the S, E, and M proteins together create the viral envelope. Among them, Spike promotes host attachment and virus–cell membrane fusion during virus infection. Therefore, Spike determines to some extent the host range[2,4,6]. Note MERS-CoV S-protein displayed very little homology toward that of SARS-CoV in the RBD domain, due to the different binding target for its S-protein, the human dipeptidyl peptidase 4 (DPP4)[17]. The entry of all coronaviruses into host cells is mediated by spike glycoprotein that gives coronaviruses a crown-like appearance by forming spikes on their surface. The amino acid sequence of spike glycoprotein made of 3 things; a large ecto domain, a single-pass transmembrane anchor, and a short C-terminal intracellular tail. A receptor-binding unit S1 and a membrane-fusion unit S2 made the ecto domain. Electron microscopic imaging illustrated that spike glycoprotein forms a clove-shaped spike with three S1 heads and a trimeric S2 stalk. For a virus to enter a host cell, S1 binds to a specific cell surface receptor via its receptor-binding domain (RBD) and S2 fuses the host cell and viral membranes, enabling the entry of viral genomes into host cells. Specific RBD-receptor binding determines if a cell or animal can be infected and also serves as a target for therapeutic inventions to treat diseases caused by coronaviruses[18].

Function of SARS COV2 Spike Glycoprotein

To gain entry into host cells, 2019-nCoV makes use of a densely glycosylated spike (S) protein. The S protein is a trimeric class I fusion protein which exists in a metastable prefusion conformation. It undergoes a substantial structural rearrangement to fuse the viral membrane with the host cell membrane. When the S1subunit binds to a host cell receptor, this process is triggered. The prefusion trimer is destabilized by binding of receptor, which results shedding of the S1 subunit and transition of the S2 subunit to a stable post fusion conformation. The receptor-binding domain (RBD) of S1 undergoes hinge-like conformational movements that transiently hide or expose the determinants of receptor binding, to engage a host cell receptor. These two states are referred to as the "down" conformation and the "up" conformation, where down corresponds to the receptor-inaccessible state and up corresponds to the receptor accessible state, which is thought to be less stable. So the S protein represents a target for antibody-mediated neutralization. It's prefusion S structure would provide atomic-level information to guide vaccine design and development[19,20]. Scientists showed that, with the most notable variation arising from an insertion in the S1/S2proteasecleavage site that results in an "RRAR" furin recognition site in 2019-nCoV rather than the single argininein SARS-CoV[19]. So far, the SARS-CoV-2 genome has been considered more stable than SARS-CoV or MERS-CoV. Another group of scientists reported in their study that there is a 382-nt deletion covering almost the entire open reading frame 8 (ORF8) of SARS-CoV-2 obtained from samples of patients in Singapore. Overwhelmingly SARS viruses had mutations or deletions in ORF8, that have been associated with reduced replicative fitness of the virus. It may be associated with host adaptation[21]. Depending on the viral species, different coronaviruses use separate domains within the S1 subunit to recognize a variety of attachment and entry receptors. Endemic human coronaviruses OC43 and HKU1 attach via their S domain A (S^A) to 5-Nacetyl-9-O-acetyl-sialosides found on glycoproteins and glycolipids at the host cell surface to enable entry into susceptible cells. MERS-CoV S, however, uses domain A to recognize non-acetylated sialoside attachment receptors, which likely promote subsequent binding of domain B (S^B) to the entry receptor, dipeptidyl-peptidase 4. SARS-CoV and several SARS-related coronaviruses (SARSr-CoV) interact directly with angiotensin-converting enzyme 2 (ACE2) via S^B to enter target cells[19].

Attachment and Entry of Virus

Receptor recognition is the first step of viral infection and is a key determinant of host cell and tissue tropism[19]. ACE2 is known to be a cell receptor for SARS-CoV[4,10,14]. High ACE2 expression was identified in type II alveolar cells (AT2) of lung, esophagus upper and stratified epithelial cells, absorptive enterocytes from ileum and colon, cholangiocytes, myocardial cells, kidney proximal tubule cells, and bladder urothelial cells. These findings indicated that those organs with high ACE2-expressing cells should be considered as potential high risk for 2019-nCoV infection[22,23]. Different study showed that spike protein of the SARS-CoV-2 virus has sufficient affinity to the ACE2 receptors of human cells to use them as a mechanism of cell entry for SARS-CoV and HCoV-NL63[4,23]. Studies have shown that SARS-CoV-2 has a higher affinity to human ACE2 than the original SARS virus strain[4]. Study proved that 2019nCoV does not use other coronavirus receptors, aminopeptidase N, and dipeptidyl peptidase 4[9]. Earlier in February, 2020 a group of scientists found that the RBD domain of the 2019-nCoV S-protein sup7ports strong interaction with human ACE2 molecules. These findings suggest that the ACE2 plays an important role in cellular entry, thus ACE2-expressing cells may act as target cells and are susceptible to 2019-nCoV infection. The expression and distribution of the ACE2 in human body may indicate the potential infection routes of 2019-nCoV[22,23]. ACE2 bound to the 2019-n-CoV S ecto domain with ~15 nM affinity, which is ~10- to 20-fold higher than ACE2 binding to SARS-CoV S[20]. Scientists also showed that ACE2 also expressed in lymphocytes within oral mucosa. The ACE2-expressing cells in oral tissues, especially in epithelial cells of tongue, might provide possible routes of entry for the 2019-nCov, which indicate oral cavity might be a potential risk route of 2019-nCov infection[23]. SARS-CoV-2 may also use Basigin (BSG)/cluster of differentiation 147 (CD147) to gain cell entry. BSG also known as extracellular matrix metalloproteinase inducer (EMMPRIN) orCD147 is a protein that in humans is encoded by the *BSG* gene. SARS-CoV-2 attaches itself to CD147 via spike protein (SP).For entry of SARS-CoV-2 initial spike protein priming by transmembrane protease, serine 2 (TMPRSS2) is essential. When a SARS-CoV-2 virion attaches to a target cell, the cell's protease TMPRSS2 cuts open the spike protein of the virus and expose a fusion peptide. The virion then releases RNA into the cell and it forces the cell to produce copies of the virus which can infect more cells. SARS-CoV-2 produces at least three virulence factors that promote shedding of new virions from host cells and inhibit immune response[4]. Attachment and entry of HCoV could be restricted by host factors like Interferon inducible trans membrane proteins (IFITMs) exhibited broad-spectrum antiviral functions against various RNA viruses. The entry of SARS-CoV, MERS-CoV, HCoV-229E and HCoV-NL63 was restricted by IFITMs. HCoV-OC43 used IFITM2 or IFITM3 as an entry factor to facilitate its infection[6].

Cytokines Related with Pathophysiology

The pathophysiology of unusually high pathogenicity for SARS-CoV or MERS-CoV has not been completely understood. Early studies have shown that increased amounts of pro-inflammatory cytokines in serum like IL1B, IL6, IL12, IFNγ, IP10, and MCP1 were associated with pulmonary inflammation and extensive lung damage in SARS patients[24]. MERS-CoV infection was also reported to induce increased concentrations of pro-inflammatory cytokines (IFNγ, TNFα, IL15, and IL17). Scientists noted that patients infected with 2019-nCoV also had high amounts of IL1B, IFNγ, IP10, and MCP1, probably leading to activated T-helper-1 (Th1) cell responses[24]. Moreover, patients requiring ICU admission had higher concentrations of GCSF, IP10, MCP1, MIP1A, and TNFα than did those not requiring ICU admission, suggesting that the cytokine storm was associated with disease severity. However, 2019-nCoV infection also initiated increased secretion of T-helper-2 (Th2) cytokines like IL4 and IL10 that suppress inflammation, which differs from SARS-CoV infection[25].

Conclusion

2019-nCoV still needs to be studied deeply because it becomes a global health threat. All three pandemic human CoVs (SARS, MERS and SARS-2) are the result of recombination among CoVs. S gene is involved in recombination of all the three viruses that binds to human receptors. Many bat CoVs are found ready to bind to human ACE2 and replication in human cells. Continuous surveillance of coronaviruses in their natural hosts and in humans is necessary to rapid control of new coronavirus outbreaks, to monitor its future host adaption, viral evolution, infectivity, transmissibility and pathogenicity.

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