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Coronavirus-19 Disease (COVID-19) Overview, History, Classification, Structure, Hosts, Interaction with its Target Cell, Transmissions and Detection

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Abstract

The COVID-19 was first officially recognized in Wuhan, China, in December 2019. Corona viruses are viruses belong to family Coronaviridae. SARS-CoV-2 is a spherical shaped and enveloped virus under beta-corona virus genus, which is 50-200 nm in diameter. SARS-CoV can infect animals such as cats, dogs and ferrets. The SARS-CoV-2 enters into the host cells by using the receptor-binding domain (RBD] of S protein that interacts with the cellular receptor angiotensin-converting enzyme 2 (ACE2]. Transmission of SARS CoV-2 to healthy individual occurs through respiratory droplets and aerosol from coughing and sneezing.

The thermal screening of visitors has become a normal response protocol since the SARS epidemic. It has been reported that the prevalence rates of co-infection of COVID-19 were above those previously reported in Wuhan, China. Disorders associated with COVID-19 include infection of neonates born to mothers with corona virus disease-2019, persisting olfactory dysfunction and exhibition of various gastrointestinal symptoms. It is incredibly important to address the potential responses of the human immune system during the SARS-CoV-2 infection. Humoral immune response, especially the production of neutralizing antibody, plays a protective role by limiting the infection at a later phase and prevents re-infection in the future. Until now, an efficient weapon against COVID-19 isn't gained by anybody. Despite the worsening trend of COVID-19, no drugs have been validated to exhibit significant efficacy in the clinical setting. The potential drugs, including remdesivir, hydroxychloroquine (HCQ], azithromycin, and immunomodulators, have not been subjected to large-scale studies or clinical trials. The aim of this paper is to make a sight on some points related to COVID-19.

Keywords: COVID-19; History; Classification; Structure; Hosts; Interaction; Transmissions; Detection; RBD; ACE2

Overview of Coronavirus-19 disease (COVID-19)

The COVID-19 was first officially recognized in Wuhan, China, in December 2019. It rapidly spread in China and became a global threat. By 7 May 2020, the causative pathogen, namely severe acute respiratory syndrome corona virus 2 (SARS-CoV-2] has infected 3,672,238 people and caused 254,045 deaths globally. A striking aspect of COVID-19 is that the disease became a pandemic in less than 3 months [1].

History of COVID-19

In 1960, the corona virus was characterized for the first time isolated from a child with upper respiratory tract infections [2]. Then, the HCoV-OC43 and HCoV-229E strains of corona viruses were identified from the persons suffering from colds [3, 4]. However, these two viruses and infectious bronchitis virus, mouse hepatitis virus, and swine transmissible gastroenteritis virus were morphologically similar under electron microscopy; therefore, this new group of viruses was named corona virus in the late 1960s [2]. The term coron used to mean crown-like structure surrounded by surface projection of the viruses under electron microscopy [2]. The HCoV-OC43 and HCoV-229E strains of corona virus cause common cold in human prevalent worldwide [2, 5]. In November 2002, corona virus (SARS-CoV] causing pandemic severe acute respiratory syndrome (SARS] was first identified in Foshan, Guangdong, China. Approximately 29 separate countries were affected by SARS-CoV and at least 831 people were 96 died worldwide among over 8000 infected cases [6]. The human corona virus NL63 (HCoV-NL63*]* was first identified in 2004 in Netherland from a seven-month-old child with bronchiolitis [7]. A novel strain of corona virus HKU1 (HCoV-HKU1] has been discovered in 2005 which was isolated and characterized from an adult human suffering from chronic pulmonary disease in Hong Kong [8]. The Middle East respiratory syndrome-related corona virus (MERS-CoV] is another species of corona virus; first reported in 2012 in Saudi Arabian patient suffering from pneumonia [9]. As of April, 2019, globally 2374 MERS-CoV confirmed cases have been reported with a total of 823 deaths from 27 countries worldwide [10]. The latest strain of a pandemic corona virus is SARS-CoV-2 which causes COVID-19; reported, 2019 in Wuhan of China on 31 December [11]. Due to extremely high contagiousness of SARS-CoV-2; as of May 20, 2020, more than 5000,000 cases of COVID-19 have been confirmed from 213 affected countries and territories with more than 334,000 deaths.

Classification of COVID-19

Corona viruses are viruses belong to family Coronaviridae. They can produce diseases in human and animal. Under this family, there are four genera; Alpha-corona virus, Beta-corona virus, Gamma-corona virus, and Delta-corona virus.

Mild illness in the upper respiratory tract can be produced by the human corona viruses while some strains are lethal and can cause severe acute respiratory syndrome (SARS], middle East respiratory syndrome (MERS] and corona virus disease 2019 (COVID-19] [6, 9, 12]. So, COVID-19 has been divided into four types: mild, moderate, severe, and critical cases [13].

Structure of COVID-19

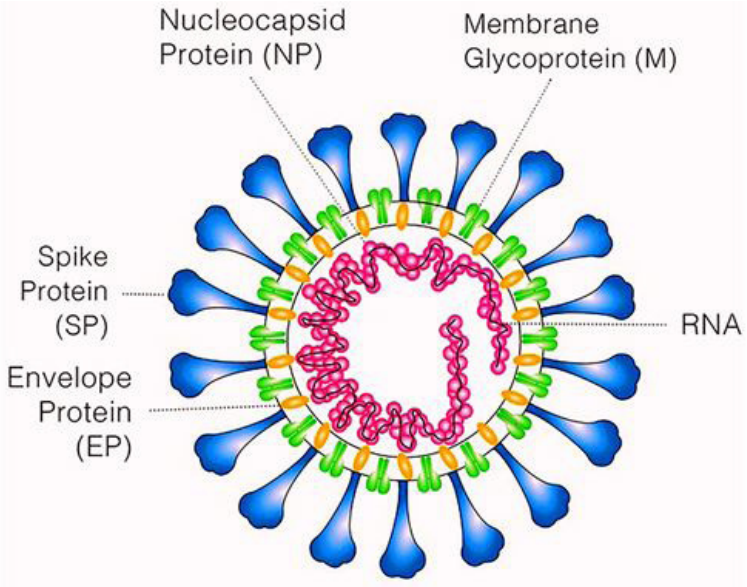

Figure 1: Structure of SARS-CoV-2

SARS-CoV-2 is a spherical shaped and enveloped virus under beta-corona virus genus, which is 50-200 nm in diameter. The viral genome is a ~30 kb sized single-stranded positive sense RNA materials from which four structural proteins and 16 non-structural proteins are produced. The structural proteins are spike (S], envelope (E], membrane (M] and nucleocapsid (N] [14]. Wu, *et al.*, 2020 indicated that the viral envelope consists of E and M proteins on which S is anchored15]] (Figure 1).

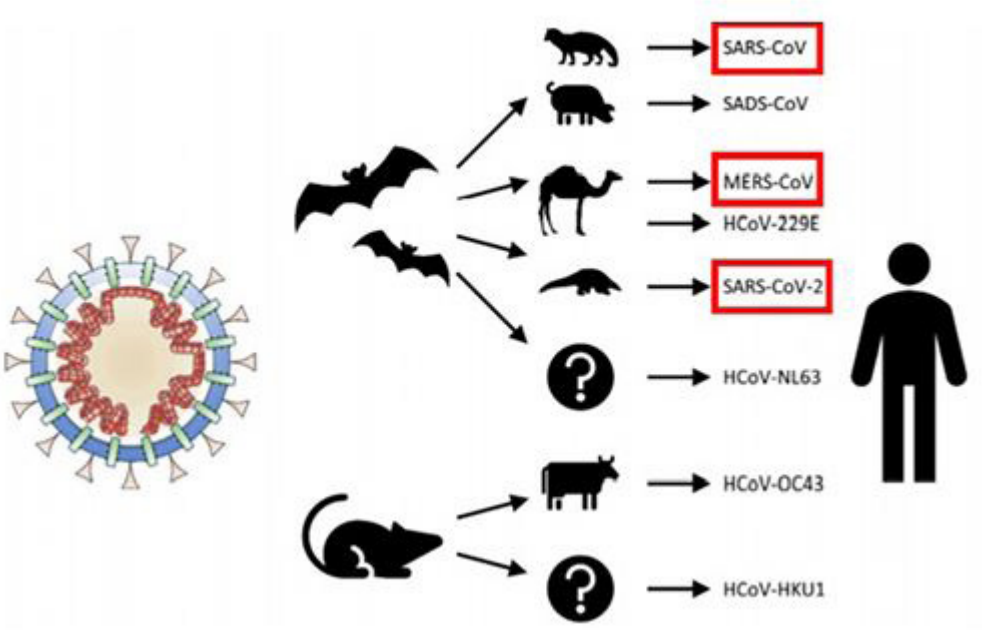

Figure 2: Animal origins of human corona viruses (SARS-CoV, MERS-CoV and SARS-CoV-2)

Hosts of COVID-19

Figure (2) show that the severe acute respiratory syndrome corona virus (SARS-CoV] and Middle East respiratory syndrome corona virus (MERS-CoV] were transmitted to humans from bats by civet cats and dromedary camels, respectively. The 2019 SARS-CoV-2 was likely transmitted to humans through pangolins that are illegally sold in Chinese markets [16, 17].

SARS-CoV can infect animals such as cats, dogs and ferrets [18, 19, 20]. However, there is very limited information regarding the investigations on SARS-CoV-2 in animals. A recent study found that SARS-CoV-2 could recognize the host cells receptor ACE2 of pigs, ferrets, cats, orangutans, monkeys, and humans with similar efficiencies [21]. Several cases of SARS-CoV-2, which causes COVID-19 in human; have been confirmed in animals. Laboratory studies also showed that cat and ferrets are highly susceptible to SARS CoV-2 that was isolated from human [22, 23]. To date, there is no published report so far on the investigation of SARS-CoV-2 in domestic pets, which were in contact with COVID-19 patients.

Corona viruses circulate in bats usually move through an intermediate animal host until crossing the boundary between organisms to infect humans [24]. Different species of bats in China carry genetically diverse corona viruses, some of which are direct ancestors of SARS-CoV [24, 25, 26]. Indeed, the first SARS-CoV that caused a human outbreak derived from SARS-like CoV circulating in Chinese horseshoe *Rhinolophus* bats which apparently adapted to wild Himalayan palm-civet before spreading in humans [27]. The MERS-CoV originated from a Pipistrellus bat CoV and was probably transmitted to humans through contact with infected camels [28, 29, 30]. Soon after the first outbreak of SARS-CoV-2 in humans, it was reported that this new virus was related to a bat-borne corona virus (BatCoV RaTG13] present in the *Rhinolophus affinis* bat species [31]. The identification of an intermediate animal hosts has been the subject of intense research and it was claimed that a pangolin (*Manis javanica*] was the intermediate host for SARS-CoV-2 [32]. The SARS-CoV-2 receptor ACE2 from bat and pangolin and several other species were found to resemble that of human [33].

Interaction of COVID-19 with its target cell

In Figure 3 the SARS-CoV-2 enters into the host cells by using the receptor-binding domain (RBD] of S protein that

interacts with the cellular receptor angiotensin-converting enzyme 2 (ACE2) [34]. The type II transmembrane serine protease (TMPRSS2] expression increases cellular uptake of the corona virus [35, 36, 37].

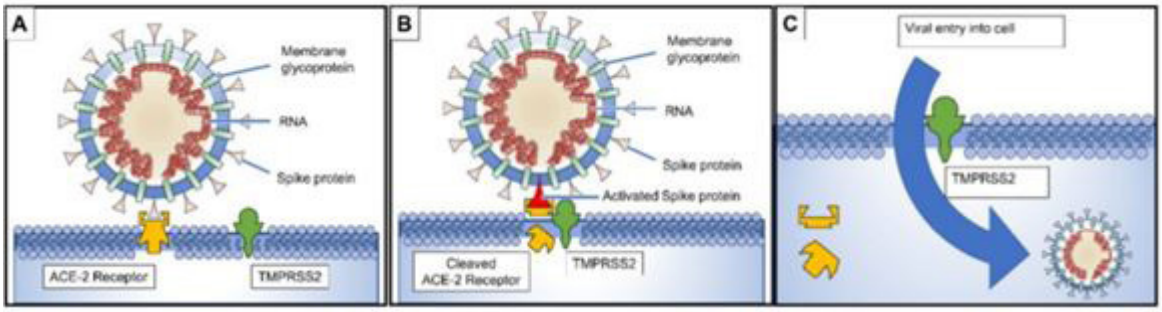

Figure 3: (A) Spike proteins on the surface of the corona virus bind to angiotensin-converting enzyme 2 (ACE-2) receptors on the surface of the target cell; (B) the TMPRSS2 binds to and cleaves the ACE-2 receptor. In the process, the spike protein is activated; (C) Cleaved ACE-2 and activated spike protein facilitate viral entry

SARS-CoV-2 has recently been documented to able to bind the alveolar pneumocytes that express ACE2 at their surface [31, 38]. Yet, in humans, the ACE2 mRNAs were found expressed in virtually all organs including the heart, blood vessels, kidney and testis, opening the possibility for this virus to infect other tissues beside lung [39, 40]. ACE2 is a known peptidase that regulates the rennin angioten-aldosterone system (RAAS], thus controlling blood pressure. It is not surprising, therefore, that initials reports indicated that hypertension, diabetes and cardiovascular diseases were the most common co morbidity in COVID-19 disease [41].

ACE2 is also expressed by the small intestine enterocytes and expected to regulate the gut antimicrobial peptides expression [42]. Moreover, this peptidase is also present on the arterial and venous endothelial cells, and arterial smooth muscle [43]. In normal human lung, the ACE2 protein is found on type I and II alveolar epithelial lung cells [44]. High expression of ACE2 has also reported on oral mucosal epithelial cells of [45].

ACE2 plays an important glycemic protective function in the pancreas [46]. Low ACE2 expression in the kidney is also associated with progressive renal diseases including diabetic nephropathy [47]. Human ACE2 mRNA expression and human ACE2 protein polymorphism influence SARS-CoV-2 susceptibility and COVID-19 disease outcome.

A for the SARS-CoV, the S1 domain of the spike protein mediates ACE2 receptor binding whereas the S2 domain is a membrane-associated portion that likely undergoes post-binding transconformational modifications allowing membrane fusion. The viral receptor binding domain (RBD] located in S1 has been narrowed down to amino acid residues 318 to 510 [48]. A point mutation Leu584Ala in ACE2 markedly attenuated the shedding of the enzyme and facilitated SARS-CoV entry into target cells [49]. A soluble form of ACE2 lacking the cytoplasmic and transmembrane domain of the molecule was reported capable of blocking binding of SARS-CoV spike protein to ACE2 [50]. Expression of ACE2 was found down regulated in cells infected by SARS-CoV [34]. A recombinant SARS-CoV spike protein was found to down regulated ACE2 expression through release of sACE2 and thereby promotes lung injury [51]. Among other antiviral effects of Chloroquine on SARS-CoV *in vitro,* a glycosylation deficit of the ACE2 virus cell surface receptor could be attributed [52, 53].

Recently, research into SARS-CoV-2 cell entry via ACE2 binding showed substantial commonalities between SARS-CoV and SARS-CoV-2 infection, including similar entry receptor selection [54]. SARS-CoV and SARS-CoV-2 share about 260 76% amino acids identity and most amino acid residues essential for ACE2 binding were conserved in the SARS-CoV-2 spike S1 domain. Another recent paper published reported the structural basis of SARS-CoV2 interaction with ACE2 [55]. The role of these isoforms in SARS-CoV-2 infection and COVID-19 outcome remains speculative.

ACE2 protein at the surface of lung alveolar epithelial cells enables SARS-CoV-2 to infect the respiratory tract. It can be hypothesized that the ACE2 levels correlate with susceptibility

to SARS-CoV-2 infection. Apparently, men have a higher ACE2 expression in lung than women and Asian people express ACE2 higher than Caucasian and African American populations [44]. This is in agreement with the finding that conversion of Ang II to Ang (1-7] by ACE2 was higher in males than female 100, suggesting an over-expression of ACE2 in men. Because ACE2 is encoded by a gene located on the X chromosome and men express more ACE2 than women it could be speculated that depending the allele expressed by women, they could be considered of lower sensitivity against the most severe adverse effects of the infection57 ,56]]. All clinical reports published to date indicate that men represent between 66% and 75% of the most severe cases of COVID-19. During early SARS-CoV-2 infection and viral spread within body tissues, the ACE2 function is likely impaired either by steric hindrance of the peptidase domain of ACE2 following virus binding or by down regulation of ACE2 mRNA expression and ACE2 protein. In severe COVID-19 disease, the presence of the viral receptor on other tissues than lung may explain the multi-organ failure sometimes observed in clinic. Therefore we recommend incorporating quantification of ACE2 and AngII be added to the COVID-19 patients biological monitoring. The mechanism f or acute myocardial injury caused by SARS-CoV-2 during serious COVD-19 disease may be linked to catalytic activity inhibition of ACE2 [58].

Transmissions of COVID-19

Transmission of SARS CoV-2 to healthy individual occurs through respiratory droplets and aerosol from coughing and sneezing [59]. Surface or feces contaminations may also involve in indirect transmission with it [15, 60, 61]. It is already reported that many of the infected patients do not show any clinical symptoms but may shed the virus through their respiratory droplets [62]. On the other hand, the infected person may shed virus before onset of the symptoms, therefore, SARS CoV-2 can be transmitted to the healthy individuals in three possible ways; symptomatically, pre-symptomatically, and asymptomatically [63]. Moreover, SARS CoV-2 might be transmitted as airborne and closed environments contribute to the secondary transmission of the virus thereby promote the super-spreading phenomenon [64, 65].

Detection of COVID-19

The thermal screening of visitors has become a normal response protocol since the SARS epidemic [66]. Fever was a common symptom, 47.4% - 100%, among patients with pneumonia caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2], [67]. Body temperature measurements once daily for healthcare workers and twice daily for people in isolation or quarantine are important measures to reduce the risk of cross infections. The HEAR Thermo, a watch-like wearable device, can measure body surface temperature and heart rate every 10 s with good reliability for testing and adequate validity of the criterion [68].

In the history of medicine, autopsies and tissue sampling have played a fundamental role in order to understand the pathogenesis of emerging diseases, including infectious ones; compared to the past, histopathology can be now expanded by innovative techniques and modern technologies. For the first time in worldwide literature, we provide a detailed postmortem and biopsy report on the marked increase, up to1 order of magnitude, of naked megakaryocyte nuclei in the bone marrow and lungs from serious COVID-19 patients. Most likely related to high interleukin-6 serum levels stimulating megakaryocytopoiesis, this phenomenon concurs to explain well the pulmonary abnormal immunothrombosis in these critically ill patients, all without molecular or electron microscopy signs of megakaryocyte infection [69].

SARS-COV-2 has arisen as a new pathogen frequently inducing sepsis-like manifestations in the host. Indeed, based on actual evidence showing hyperinflammation as well as T cell deficiencies and coagulation abnormalities, associated with life-threatening organ dysfunction, severe COVID-19 may be well consistent with a clinical diagnosis of viral sepsis, rather than with a mere hyperinflammatory disease. This conceptual framing may help to improve clinical management of severe COVID-19 patients, by providing a rationale for the development of novel balanced immunomodulatory approaches, combining both suppressive and activating immunotherapies [70].

The main focus of Coronavirus disease 2019 (COVID-19) infection is pulmonary complications through virus-related neurological manifestations, ranging from mild to severe, such as encephalitis, cerebral thrombosis, neurocognitive (dementia-like) syndrome, and delirium. The hospital screening procedures for quickly recognizing neurological manifestations of COVID-19 are often complicated by other coexisting symptoms and can be obscured by the deep sedation procedures required for critically ill patients. Here, we present two different case-reports of COVID-19 patients, describing neurological complications, diagnostic imaging such as olfactory bulb damage

(a mild and unclear underestimated complication) and a severe and sudden thrombotic stroke complicated with hemorrhage with a low-level cytokine storm and respiratory symptom resolution. We discuss the possible mechanisms of virus entrance, together with the causes of COVID-19-related encephalitis, olfactory bulb damage, ischemic stroke, and intracranial hemorrhage [71].

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