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COVID-19: AN ENIGMA WHICH HAS ENGULFED THE WORLD

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ABSTRACT

Chinese health authorities in late December 2019 reported an outbreak of pneumonia of unknown origin in Wuhan, Hubei Province. Following the outbreak of pneumonia of unknown origin, the genome of a novel coronavirus was released (http://viro-logical.org/t/novel-2019-coronavirus-genome/319; Wuhan-Hu-1, GenBank accession No. MN908947) and was made publicly available to the scientific community. This novel coronavirus was provisionally named 2019-nCoV which was later on calledSARS-CoV-2. Since its discovery, the virus has spread globally, leading to fatalities in more than 1 lakh and more than 19 lakhs being infected, leading to a massive impact on the world's health systems and economies. In this review, the current knowledge about the epidemiology, phylogenetic, molecular diagnostics and drug strategies against COVID 19 has been summarized.

Keywords:

COVID-19; Pandemic; Phylogenetic; Real-time polymerase chain reaction; SARS-CoV-2

INTRODUCTION

Towards the end of December 2019, there was an outbreak of pneumonia of unknown origin in the city of Wuhan, Hubei Province, China which was epidemiologically traced to the Huanan Seafood Wholesale Market. Following the inoculation of the broncho-alveolar lavage fluid obtained from the suspected patients into the human airway epithelial cells, Vero E6 and Huh7 cell lines led to the isolation of a novel coronavirus, SARS-CoV-2, previously named 2019-nCov [1].

Coronaviruses are positive single-stranded RNA viruses surrounded by an envelope and they belong to the family Coronaviridae. The Coronaviridae family is divided into four genera: Alpha-, Beta-, Gamma-, and Delta coronavirus out of which seven human coronaviruses (HCoVs) have been identified, falling within the Alpha- and Betacoronavirus genera. The Alphacoronavirus genus includes HCoVNL63 and HCoV-229E, while the Betacoronavirus genus comprises HCoV-OC43, HCoV-HKU1, SARS-CoV (severe acute respiratory

syndrome coronavirus), MERSCo V (Middle East respiratory syndrome-related coronavirus), and the novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) [2–7]. The alphacoronaviruses HCoV-NL63 and HCoV-229E and the betacoronaviruses HCoV-OC43 and HCoV-HKU1 are the ones not only responsible for the occurrence of common colds, but also of severe lower respiratory tract infections, especially in the elderly and children [8].

The SARS-CoV-2 like the SARS COV implicated in the 2003 SARS outbreak is a member of the subgenus Sarbecovirus (Betacoronavirus genus lineage B) [9, 10]. Its RNA sequence is approximately 30,000 bases in length. However, the unique feature of SARS-CoV-2 is the presence of a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses [11, 12, and 13].

On the 11th of February 2020, the International Committee on Taxonomy of Viruses (ICTV) announced that as per the existing rules that compute hierarchical relationships among coronaviruses on the basis of five conserved sequences of nucleic acids, the differences between the SARS COV and SARS COV 2 were insufficient to make them separate viral species. Therefore, they identified SARS COV 2 as a strain of *Severe acute respiratory syndrome-related coronavirus*[14].On 11 March 2020, the COVID 19 caused by the SARS COV 2 was declared as a Pandemic by the World Health Organization [15].

STRUCTURAL BIOLOGY

Each SARS-CoV-2 virion is approximately 50–200 nanometres in diameter [16] having four structural proteins, known as the S (spike), E (envelope), M (membrane) and N (nucleo-capsid) proteins,where the N protein holds the RNA genome, and the S, E, and M proteins together create the viral envelope [17]. The spike protein, whose structure has been determined using cryogenic electron microscopy [18, 19], is the protein responsible for allowing the virus to attach to and fuse with the membrane of a host cell [17],.

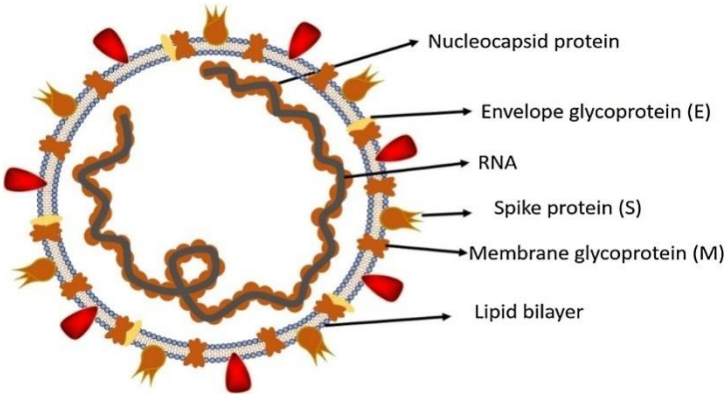

Figure 1: Structure of respiratory syndrome causing human coronavirus.

Protein modelling experiments on the spike protein of the virus suggest that SARS-CoV-2 has sufficient affinity to the receptor of the angiotensin converting enzyme 2 (ACE2) on human cells to use them as a mechanism of cell entry [19]. Moreover, it has now been shown that SARS-CoV-2 has a higher affinity to human ACE2 than the original SARS virus strain [18, 20].

Initially the priming of the spike protein by the transmembrane protease, serine 2 (TMPRSS2) is essential for entry of SARS-CoV-2 [21]. When the SARS-CoV-2 virion attaches to a target cell, the cell's protease TMPRSS2 cleaves open the spike protein of the virus, exposing a fusion peptide. The virion then releases RNA into the cell, hijacking the cell to produce copies of the virus that are disseminated to infect more cells [21].

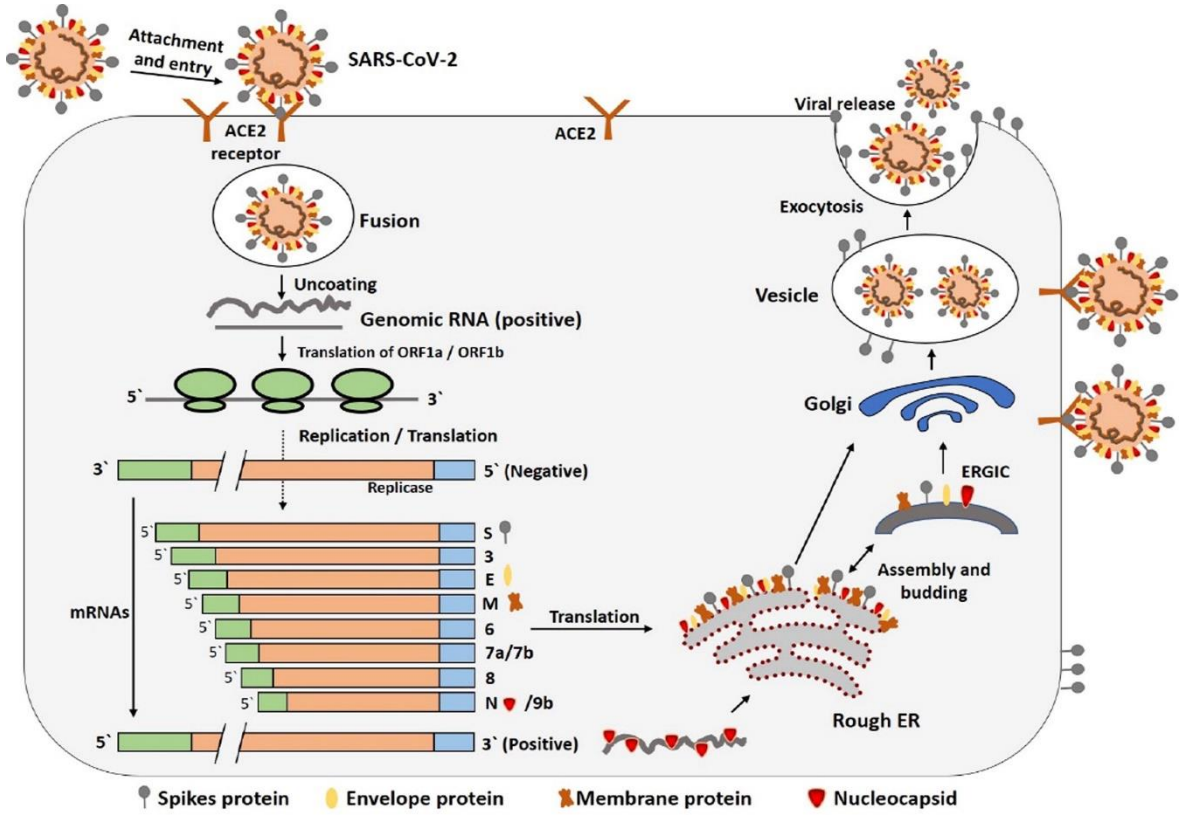

Figure 2: The life cycle of SARS-CoV-2 in host cell begins when the S protein binds to the cellular receptor ACE2. After receptor binding, the conformation change in the S protein facilitates viral envelope fusion with the cell membrane through the endosomal pathway following which the SARS-CoV-2 releases RNA into the host cell. Genome RNA is then translated into viral replicase poly-proteins pp1a and 1ab, which are then cleaved into small products by viral proteinases. The polymerase produces a series of sub-genomic mRNAs by discontinuous transcription and finally translated into relevant viral proteins. Viral proteins and genome RNA are subsequently assembled into virions in the ER and Golgi and then transported via vesicles and released out of the cell. ACE2, angiotensin-converting enzyme 2; ER, endoplasmic reticulum; ERGIC, ER–Golgi intermediate compartment [22].

SARS-COV-2 EPIDEMIOLOGY

Patients infected with SARS-CoV-2 can present a wide range of symptoms ranging from mild to severe in which fever, cough, and shortness of breath are the most common symptoms reported in 83, 82, and 31% of patients respectively [23]. However, multiple mottling and ground-glass opacity are observed on chest X-ray on those patients who develop pneumonia [23]. Patients that develop acute respiratory distress syndrome may worsen rapidly and die of multiple organ failure [23].

Gastrointestinal symptoms such as vomiting, diarrhoea, and abdominal pain have also been reported in about 2–10% of the patients with COVID-19 [23, 24]. Diarrhoea and nausea preceded the development of fever and respiratory symptoms in about 10% of patients [23]. Human to human transmission via droplets is the main route of transmission within a susceptible population. Another route of possible viral transmission is the oral-faecal route. SARS-CoV-2 was detected in stool of patients with COVID-19 pneumonia, as well as in respiratory samples [25]. Thus, it is plausible that SARS-CoV-2 can be transmitted via the oral-faecal route as well as via fomites.

MOLECULAR DIAGNOSIS OF SARS-COV-2

Confirmation of cases with suspected SARS-CoV-2 infection is performed by detection of unique viral sequences with nucleic acid amplification tests such as quantitative reverse real-time PCR (QRT-PCR) for which three assays have been developed. The first-line assay targets the E gene encoding for the envelope protein, which is common to the Sarbecovirus subgenus, while the second specific assay targets the RdRp gene encoding for RNA-dependent RNA polymerase. This assay contains two probes: one probe, which reacts with the SARS-CoV and SARS-CoV-2 RdRp gene, and a second probe (RdRP_SARSr-P2) which is specific to SARS-CoV-2. Finally, the third additional confirmatory assay targets the nucleocapsid (N) gene. However, this last assay has not been further validated because it is slightly less sensitive [26]. This protocol has been adopted in more than 30 European laboratories [27]. Recently, a novel rRTPCR assay targeting a different region of the RdRp/Hel gene of SARS-CoV-2 has been developed that showed a higher sensitivity and specificity than the RdRp-P2 assay [28].

VACCINES FOR SARS-COV-2

Though there is currently no available vaccine against COVID-19,few vaccines in the pipeline are there effective against SARS-CoV-2. Some of the vaccine candidates under various phases of development are; the mRNA based vaccine prepared by the US National Institute of Allergy and Infectious Diseases against SARS-CoV-2 [29], INO-4800- DNA based vaccine [30]. An inactivated virus vaccine is being developed by the Chinese Centre for Disease Control and Prevention (CDC) [31, 32]. Stermirna Therapeutics is working on

anmRNA based vaccine[33]. GeoVax-BravoVax is working to develop a Modified Vaccina Ankara (MVA) based vaccine [34] and Clover Biopharmaceuticals is developing a recombinant 2019-nCoV S protein subunit-trimer based vaccine [35].

POTENTIAL THERAPEUTIC STRATEGIES AGAINST COVID-19

Currently, there is no drug candidate approved for the treatment of COVID 19. Initially, interferons-a nebulization, broad-spectrum antibiotics, and anti-viral drugs were used to reduce the viral load [36, 37, 38], however, only remdesivir has shown promising impact against the virus [39]. Remdesivir only and in combination with chloroquine or interferon beta significantly blocked the SARS CoV- 2 replication and patients were declared as clinically recovered [38, 40]. Recently, doctors in Shanghai isolated the blood plasma from clinically recovered patients of COVID-19 and injected it in the infected patients who showed positive results with rapid recovery [41].

CONCLUSION AND PERSPECTIVE

The novel coronavirus that originated from the Hunan seafood market at Wuhan, China where bats andother wildlife animalswere being sold, has now rapidly spread up to 109 countries with 19,29,633 infected cases being diagnosed, 1,19,785 having died but also 4,53,018 getting recovered from COVID 19 till date. Though a zoonotic source of origin of SARS COV 2 has not been determined yet as per phylogenetic analysis,SARS-CoV is closer to SARS-like bat CoVs.

Till date, no promising clinical treatments or prevention strategies have been developed against COVID 19. However, various broad-spectrum antivirals previously used against influenza, SARS and MERS coronaviruses are now been evaluated either alone or in combinations to treat COVID-19 patients, mice models, and clinical isolates. The need of the hour is to develop rapid and accurate diagnostic methods, revamp the medical facilities around the world and to develop therapeutics against COVID 19.

COMPETING INTERESTS

The authors declare no competing interests.

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