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Succinct review on Biological and Clinical Aspects of Coronavirus Disease 2019 (COVID-19)

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Abstract

The prevalence of coronavirus disease 2019 (COVID-19) is the third registered spillover of an animal coronavirus to humans from the early 21st century. Coronaviruses are important human and animal pathogens. The 2019 novel coronavirus (2019-nCoV) rapidly spreads, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. Recently, a wide range of inhibitors have been introduced for treatment of COVID-19, and also promising vaccines are in late phase of development. Here, we aim to present an overview of recent findings of the biological and clinical aspects of SARS-CoV-2 infection, along with possible treatments and future vaccines.

Keywords: COVID-19; Immune response; Diagnosis; Treatments; SARS-CoV-2

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) is the third registered spillover of an animal coronavirus to humans from the early 21st century. Before the outbreak of SARS-CoV (severe acute respiratory syndrome coronavirus) infection within 2002-2003 in the Guangdong province, China, coronaviruses were considered to be slightly pathogenic to humans. MERS-CoV (Middle East respiratory syndrome coronavirus) is another highly pathogenic coronavirus that appeared in the Middle Eastern countries ten years after the outbreak of SARS-CoV. Recently, in December 2019, a new coronavirus from 3 patients with pneumonia was discovered and termed 2019 novel coronavirus (2019-nCoV). All three patients were somehow related to the wet animal and seafood wholesale market in Wuhan, Hubei Province, China. Afterward, the virus was named as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). SARS-CoV-2 is an enclosed virus with positive single-stranded RNA belonging to Betacoronaviruses, which can infect both humans and animals. The biological behavior of SARS-CoV-2 is mostly the same as SARS-CoV and MERS-CoV. SARS-CoV-2 uses the same structural protein as SARS-CoV and MERS-CoV, to gain entry to the host cells.

Figure 1. This figure represents an epidemiological comparison between COVID-19 and other well-known respiratory viral infections. The average basic reproduction number (R0) is an epidemiologic metric that describes the transmissibility of infectious agents. R0 measures the expected number of secondary infections produced by a single infectious individual in a susceptible population during the mean infectious period. Case Fatality Ratio (CFR) indicates the proportion of episodes of disease that are fatal. Created with BioRender.com

The patients with SARS-CoV-2 mostly have symptoms such as fatigue, fever, dry cough, and dyspnea. Clinical and laboratory evaluation, along with chest CT scan and real-time RT-PCR (real-time reverse transcription-polymerase chain reaction) assay, can help to confirm the disease. Since SARS-CoV-2 has no particular vaccine or cure, patients are better to be hospitalized soon after diagnosis to receive proper health care. However, recently a wide range of inhibitors have been introduced for treatment of COVID-19. Furthermore, promising vaccines are in late phase of development. Here, we aim to present an overview of recent findings of the biological and clinical aspects of SARS-CoV-2 infection, along with possible treatments and future vaccines. Using various sources, including CDC, WHO, and some journals we have concisely provided an epidemiological comparison between COVID-19 and other well-known respiratory viral infections in [Figure 1].

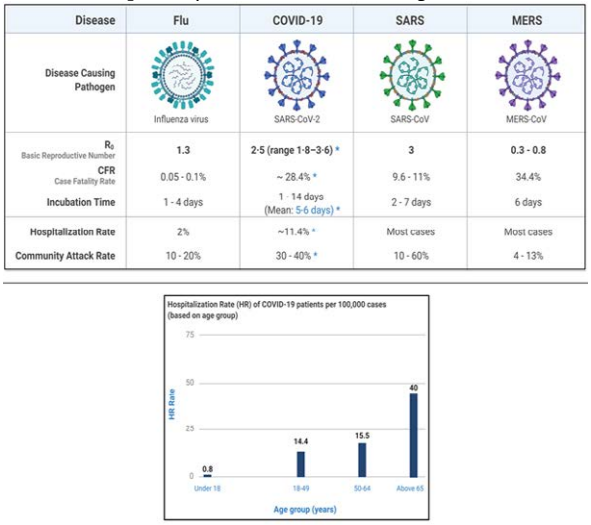

Figure 1: Study flow chart of recruiting of hypoglycemic patients and matched normoglycemic patients (PGBH=post gastric bypass hypoglycemia, MMT=mixed meal test).

Phylogeny and Origin of Coronaviruses

The Coronaviridae Study Group (CSG) of the International Commit-

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tee on Taxonomy of Viruses (ICTV) determined that coronaviruses related to the subfamily of Coronavirinae in the family Coronaviridae and the order Nidovirales. Based on phylogenetic relationships and genomic structures, this subfamily contains 4 genera, including Alphacoronavirus, Gammacoronavirus, Betacoronavirus, and Deltacoronavirus. The Betacoronaviruses have four lineages (A, B, C, and D). SARS-CoV and SARS-CoV-2 belong to lineage B, and lineage C includes MERS-CoV. According to phylogeny and taxonomy, the CSG placed 2019-nCoV, within the Coronaviridae [Figure 2]. Given this, they termed this SARS-CoV-2 (severe acute respiratory syndrome-related coronavirus). There are three extremely pathogenic coronaviruses, SARS- CoV, MERS-CoV, and SARS-CoV-2, leading to a severe respiratory syndrome in humans. It is proposed that both MERS-CoV and SARS-CoV have originated from bats. MERS-CoV and SARS-CoV have infected humans through direct transmission from civets and dromedary camels, respectively, which seem to be the intermediate hosts for these viruses. It has been confirmed that these viruses are capable of human-to-human transmission. Phylogenetic analysis showed that 2019-nCoV has more than 88% identity to the genome of two types of coronaviruses originated from bats, bat-SL-CoVZXC21 and bat-SL-CoVZC45. However, it has less genome similarity to MERS-CoV (~50%). SARS-CoV-2, in comparison to SARS-CoV, has been considered to be a new human-infecting betacoronavirus due to its distinct genetic characterizations. At first, skeptic views were whispered that this virus is a product of purposeful manipulation, but a comprehensive analytical study explicated that this is not a laboratory constructed virus [1-4] [Figure 3].

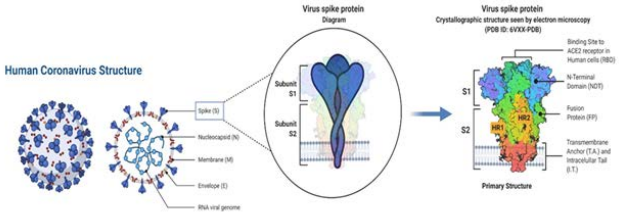

Figure 2: Axial view of the VOI on MIM software of hypoglycemic participant 3 (a+b) and normoglycemic match 3 (c+d).

Structure and life-cycle of SARS-CoV-2

SARS-CoV-2 genome contains 29,881 bp in length with 14 open reading frames (ORFs) encoding 27 proteins. The 3′-terminus of the genome comprises of sequences for encoding 8 accessory proteins (3a, 3b, 7a, p6,7b, 8b, 9b, and orf14), and 4 main structural proteins, including spike surface glycoprotein (S), an envelope protein (E), matrix protein (M), and nucleocapsid protein (N). Despite the relationship between SARS-CoV-2 and SARS-CoV, there are some distinct differences at the amino acid level. For example, unlike SARS-CoV, the 8a protein is absent in SARS-CoV-2; the 8b protein in SARS-CoV-2 is longer in contrast to SARS-CoV; in comparison to SARS-CoV, the 3b protein is considerably shorter in SARS-CoV-2. The pp1ab and pp1a proteins of the SARS-CoV-2 are encoded by ORF1a and ORF1ab genes situated at the 5′-terminus of the genome, respectively [5].

Unlike MERS-CoV that binds to dipeptidyl peptidase 4 (DPP4; also called CD26) to infect the unciliated bronchial epithelial cells as well as pneumocytes type II, both SARS-CoV and SARS-CoV-2 are linked to ACE2 (angiotensin-converting enzyme 2) on pneumocytes type II and ciliated bronchial epithelial cells. Though SARS-CoV-2 and SARS-CoV have similar receptor-binding domain structure, the variation of the amino acids at some key residues distinct them from each other. Based on biophysical and structural studies on S protein, the SARS-CoV-2 S protein demonstrated a greater affinity to ACE2 than SARS-CoV S protein. Since the S protein is a quintessential part of the virus life-cycle, it can be a consensus target antigen, which could be inhibited by drugs such as Arbidol. Analytical studies have delineated the SARS-CoV-2 mutations, indicating that these may have led to higher infectivity of the virus as a result of natural selection [6]. Although SARS-CoV-2 has come with higher infectivity and transmissibility than SARS-CoV, it seems to have less mortality rate. The virus life cycle initiates with the binding of SARS-CoV S protein to the ACE2 receptor and recruiting the cellular protease TMPRSS2 in order to enter the host cell via the endosomal path. A report betokened that a particular mutation (N501T) could promote interaction of the virus receptor-binding domain with human ACE2. The virus releases the genomic RNA into the cytoplasm, following the viral entry into the host cell. The next step is the translation of ORF1a and ORF1ab for producing pp1a and pp1ab polyproteins, then here proteases encoded by ORF1a cleave pp1a and pp1ab to provide the NSPs. These NSPs form the RNA replicase–transcriptase complex, which leads to producing negative-sense RNAs [7]. Further, negative-sense RNA is used as a template to produce full-length positive RNA genomes. During transcription, subgenomic RNAs like ones responsible for structural proteins (S, E, and M) produced through a process called discontinuous transcription, which afterward introduced into the endoplasmic [8][Table 1].

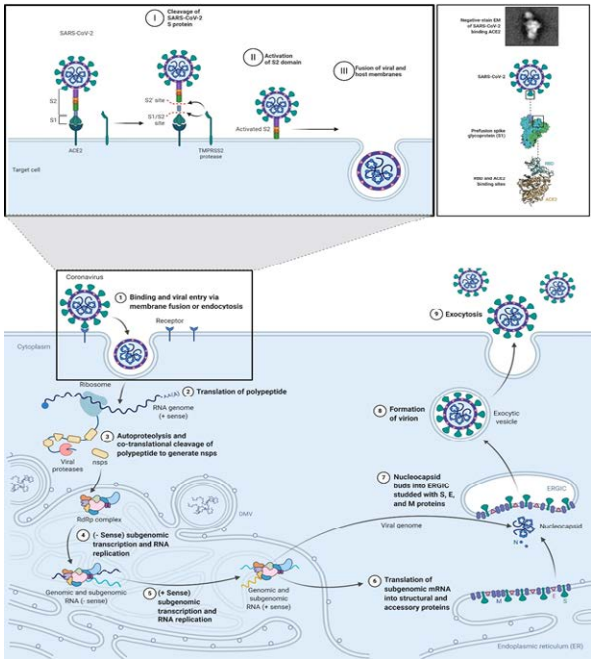

Figure 3: (a) SUVsum of pancreas and duodenum in patients (1-5) with post gastric bypass hypoglycemia

Developer	Candidate/ Mediator	Vaccine characteristics	Trial ID
Moderna	mRNA-1273	Encapsulated mRNA encoding S protein	NCT04387656
CanSino Biologicals	Ad5-nCoV	Adenoviral vector expressing S protein	NCT04398147

Pfizer	BNT162b1	RNA vaccine	NCT04368728
	BNT162b2		
	BNT162b3		
Inovio Pharmaceuticals	INO-4800	DNA plasmid encoding S protein	NCT04336410
University of Oxford	ChAdOx1 nCoV-19	Chimpanzee adenovirus-vectored vaccine expressing the SARS-CoV-2 spike protein	NCT04400838
Shenzhen Geno-Immune Medical Institute	LV-SMENP-DC	Modified dendritic cells with lentiviral vectors expressing SARS-CoV-2 proteins- administered with antigen-specific cytotoxic T lymphocytes	NCT04276896

Table 1: Different clinical-phase vaccine candidates for COVID-19

Reticulum (ER). Sub-genomic mRNAs might hold multiple ORFs, but only the one that is closest to the 5′ end (first ORF) goes to be translated. Next, these structural proteins (E, M, and S) move to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC), where they combine with viral RNA genomes encapsidated by N protein to form mature virions. Herein, The M protein has an essential role in protein-protein interaction for viral assembly. Eventually, virions use the exocytosis process to be released out of the infected cell. ORF1a and ORF1ab genes together encode 16 to 17 NSPs (non-structural proteins), including NSP1 to NSP10, NSP12, and NSP16. Two of which are proteases, namely 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro), that are being considered as invaluable drug targets. Owing to 96% homology within the sequence of 3CLpro in SARS-CoV and SARS-CoV-2 genomes, formerly introduced 3CLpro inhibitors, including peptidomimetic acrylester (PDB: 6LU7), aldehydes, isatines, a-ketoheteraromates, pyrazolidinone, Nitroanilides, ML188, racemic, and ML300 might be beneficial start-point drugs in the treatment of COVID-19 as well. Besides, machine-learning-based approaches have been put in to work to find 3CLpro inhibitor compounds (drug repurposing) [8]. Using Plant-based medicines like Flavonoids, as well as HIV protease inhibitors like lopinavir and ritonavir, have also been suggested as a 3CLpro inhibition-based treatment. Imperativeness of PLpro for the CoV replication and PLpro-mediated subterfuge from the immune system makes this protease an attractive drug target. To this end, compounds interacting with active-site Cys112, including epoxyketones, a-halo-ketone, aldehydes, alkynes, and activated esters, have been proposed as potential inhibitors. Accordingly, a drug for chronic alcohol dependency called Disulfiram has been reported to be a potential PLpro inhibitor. Alongside that, 6-mercaptopurine and 6-thioguanine as antimetabolite drugs also have the capability to inhibit PLpro. Other than those two proteases, the RNA-dependent RNA polymerase (RdRp), which recruits cell machinery to transcribe the virus genome into new RNA copies, can be an outstanding drug target. An RNA polymerase inhibitor called Favipiravir, which is mostly used in the treatment of influenza, has shown to be effective against other RNA viruses as well. It is noteworthy that Favipiravir would not restrict host DNA and RNA synthesis. Its effectiveness and minor side effects on patients with COVID-19 has been reported from a study on 70 patients in Shenzhen, Guangdong province. Remdesivir is a broad-spectrum antiviral drug that acts as an adenosine analog and thus capable of terminating the RNA synthesis in multiple RNA viruses, including SARS-CoV-2 and Ebola [9]. A preliminary randomized trial on the 1059 COVID-19 patients (538 assigned to Remdesivir and 521 to placebo) delineated that Remdesivir was superior to placebo in reducing the recovery time in adults. Remdesivir also lowered the COVID-19-related mortality rate. Another adenosine-analog drug is Galidesivir that has been administered for Ebola and Marburg virus. Moreover, A molecular docking study showcased that it has broad-spectrum antiviral activity upon RNA viruses such as SARS-CoV-2. Moreover, a machine-learning-based approach has offered AP2-associated protein kinase 1 (AAK1), and Cyclin G Associated Kinase (GAK) inhibitors, including Baricitinib (a drug approved for rheumatoid arthritis), Fedratinib, Sunitinib, and Erlotinib, to inhibit viral endocytosis. Additionally, Baricitinib can also inhibit JAK1/2, which attenuates inflammation [10].

Immune responses to SARS-CoV-2

The immune system naturally triggers an immune response against invaders like viruses. Chemotactic factors have a critical role in viral infections due to their effect to summon the leukocytes to the site of infection. So, spectral alteration in chemotactic factors may result in adverse immune responses. As mentioned before, SARS-CoV-2 mostly affects the lungs, so it should be considered that uncontrolled immune response may lead to functional impairment of lungs, pulmonary tissue damage, and reduced lung capacity. In contrast, an inadequate immune response may also intensify viral replication, which also leads to tissue damages. The host cell possesses various pattern recognition receptors (PRRs) that serve as a part of the innate immune system for recognizing the PAMPs (pathogen-associated molecular patterns). PRRs including RIG-I-like receptor (RLR), toll-like receptor (TLR), C-type lectin-like receptors (CLmin), and NOD-like receptor (NLR) are located on the cell surface. On the other hand, some PRRs are in the cytoplasm, such as cyclic GMP-AMP synthase (cGAS), IFI16, interference stimulator of interferon gene (STING), DNA-dependent activator of IFN-regulatory factor (DAI). Among them, RLRs, including MDA5 (IFIH), H family members RIG-I (DDX58), and LGP2, have the potential to recognize RNA viruses, like coronavirus. The adaptive immune responses consist of the immune response of T cells, humoral immune responses, and antibody responses. Around 80% of lymphocytes that infiltrate in the pulmonary interstitium in coronavirus infection are CD8+ T cells, which can clear the virus-infected cells and also able to induce tissue damage. It has been noted that the weakening of CD4+ T cells may cause severe interstitial pneumonitis, and delayed elimination of the virus from lungs are due to decreased pulmonary recruitment of lymphocytes and neutralization antibody and cytokine production related to the reduction of CD4+ T cells. Lymphopenia is a hallmark in patients infected with SARS-CoV and SARS-CoV-2. A study revealed that SARS-CoV E protein interaction with an antiapoptotic protein called Bcl-xL induces T-cell apoptosis. Further, it was shown that interaction of SARS-CoV E protein with Bcl-xL is mediated by BH3 (Bcl-2 homology domain 3)-like region placed in the C-terminal cytosolic domain of SARS-CoV E protein.

In addition, memory T-cell response to the structural viral proteins such as S, M, and N, demonstrated to be long-lasting (over 11 years post-infection), which could be promising to design a vaccine for the virus. SARS-CoV-2 not only infects lungs but also can cause heart injury because the ACE2 receptor is also expressed in the cardiovascular system. Along with this, it is stated that the imbalance immune response between type 1 and type 2 T-helper lymphocytes in SARS-CoV-2 infection might induce a cytokine storm, which not only affects lungs but also can cause injury to the cardiovascular system. Reports indicated that the patients with SARS-CoV-2 from Wuhan, China, had a high concentration of pro-inflammatory cytokines in their plasma, including high levels of IL1B, IL-6, IFNγ, IP10, and MCP1 that could be associated with disease severity. Patients with SARS-CoV-2 infection compared to SARS-CoV infection seem to have a greater amount of T-helper 2 cytokines such as IL4 and IL10 that quell inflammation. Studies on CoV have shown that pro-inflammatory cytokines (e.g., IFNγ, IL12, IL1B, IL6, IP10, and MCP1) are related to pulmonary inflammation and immense damage to the lungs. However, more investigations are required to determine the Th1 and Th2 responses in SARS-CoV-2 infection. Furthermore, antibodies and the complement system as part of humoral immune responses are both vital, especially during the persistent phase of CoV infection. However, the complement system has the potential to damage the host tissue at the site of infection. SARS-CoV-2 can induce a massive chain of inflammatory responses through initiating JAK/STAT signaling pathway, as well as and NF-κB, which can cause a pro-inflammatory cytokine storm. Noteworthy, that cytokines like IL-6 has a positive feedback loop and bind to their receptors and initiate a JAK/STAT-mediated signaling pathway. The virus also downregulates ACE2 receptors, which is followed by the elevation of angiotensin II and subsequently, induction of the JAK/STAT signaling pathway. This SARS-CoV-2 induced inflammatory response not only affects the lungs but also leads to cardiovascular implications. In this regard, some targeted drugs have been suggested, for example, Tocilizumab and Sarilumab as IL-6 receptor antagonists, Baricitinib, Fedratinib, and Ruxolitinib as JAK/STAT inhibitors, and serine protease inhibitors for inhibiting of NF-κB signaling pathway. Since the pandemic emerged, to this day, the knowledge about SARS-CoV-2 pathogenesis has become more elucidated. To control immune response-related injury to the lungs mediated by SARS-CoV-2, Dexamethasone has been applied as a treatment to alleviate inflammation-mediated lung injury in hospitalized patients. In which case, co-administration of Dexamethasone and respiratory support in 2104 patients indicated a lower mortality rate compared to the group who received no respiratory support.

Clinical features, Diagnosis, and Management of COVID-19

Different studies on patients demonstrated the clinical characteristics of COVID-19. According to epidemiological, demographic, clinical, laboratory, and radiological data, which includes a broad range of clinical manifestations, the most common symptoms are fever, fatigue, dry cough, dyspnea, myalgia, and shortness of breath. Less common symptoms, which mostly occurred in critically ill patients, include headache, confusion, chest pain, expectoration, pharyngalgia, diarrhea, nausea, and vomiting. Most patients showed more than one symptom. Some patients presented organ dysfunction, such as ARDS (acute respiratory distress syndrome), acute renal injury, and acute respiratory injury. There were underlying complications among reported cases, which included hypertension, diabetes, cardiovascular disease, malignancy, chronic liver disease, cerebrovascular disease, chronic kidney disease, and HIV infection. Intriguingly, Dorgalaleh et al. have reported that patients with severe hypocoagulable conditions like patients with congenital bleeding disorders might become protected from adverse effects of COVID-19-pertained hypercoagulopathy. In a study on 138 Chinese patients with COVID-19, thorough laboratory tests included prothrombin time (PT), activated partial thromboplastin time (APTT), complete blood count (CBC), D-dimer, creatine kinase (CK), CK-MB, alanine aminotransferase (ALT), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), aspartate aminotransferase (AST), total bilirubin, creatinine, hypersensitive troponin I, and procalcitonin were conducted. Prolonged PT, lymphopenia, and elevated LDH were among the most common laboratory findings. The patients in the intensive care unit (ICU), in comparison to non-ICU patients, showed more laboratory abnormalities. Patients who were in ICU showed higher levels of white blood cell (WBC) and neutrophil, D-dimer, CK, and creatine. Laboratory parameters in patients with novel coronavirus–infected pneumonia (NCIP) showed differences