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Review Article

SARS-CoV-2: Pathogenesis, Evolution and Ongoing Efforts in Drug and Vaccine Development

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ABSTRACT

The world is currently battling a pandemic disease that is spreading rapidly due to severe acute respiratory syndrome coronavirus 19 (SARS-CoV-2) that belongs to a family of coronaviruses. As per 20th December 2020, more than 77 million people have been infected with more than 1.7 million fatality cases reported worldwide. In response to this Pandemic, several efforts are being put in place to identify possible remedies, including therapeutic agents and against this virus. Currently, there is no approved vaccine or drugs against the virus, even though some countries such as Japan have approved the investigational drug Remdesivir as a coronavirus regimen. Other drugs such as chloroquine, which is widely used in treatment, remains controversial as there is no scientific evidence that establishes its effectiveness in the control of SARS-COV-2. This review constitutes a summary of SARS-COV-2 genomics and evolutionary relationship to other viruses, pathogenicity, transmission as well as efforts that have been made in the development of drugs and vaccines against this virus. We envisage that this review will provide an insightful and extensive coverage on the virus as well as support researchers in vaccine development and effective treatment protocol.

Keywords: *Coronavirus, COVID-19, SARS-COV-2, pandemic, acute pneumonia*

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INTRODUCTION

Acute respiratory infections (ARI) constitute the most common diseases in humans with a high morbi-mortality rate, mostly in children. Clinical manifestations usually range from mild, uncomplicated upper respiratory tract illness to severe lower respiratory tract infections such as pneumonia, bronchiolitis, and croup (Treanor, 2017). Most etiological agents of ARI are viruses (Treanor, 2017). To date, eight human respiratory viruses including adenovirus (ADV), bocavirus (BoV), coronavirus (CoV), metapneumovirus (MPV), parainfluenza virus (PIV), respiratory syncytial virus (RSV), rhinovirus (RV), and severe acute respiratory coronavirus (SARS-CoV) are associated with ARI (Walker *et al*., 2013). For this review, we focus particularly on the severe acute respiratory associated with coronaviruses, which have recently emerged and threatened the public health worldwide.

The coronaviruses belong to the Coronaviridae family, which consists of enveloped, positive single-stranded RNA viruses with a large genome ranging between 26-31Kb in length (Su *et al*., 2016). They cause diverse symptoms, including pneumonia, fever, breathing difficulty, and lung infection in humans (WMHC, 2020) and other mammals (Adhikari *et al*., 2020). Interest in coronavirus, particularly on the coronavirus genetic diversity and genomics, has increased worldwide just after the SARS epidemic from southern China in 2003 (Liu *et al*., 2005). To date, 7 CoVs species are known to infect humans; they include two αCoV (HCoV-229E and HKU-NL63) and four βCoV (HCoV-OC43, HCoV-HKU1, SARS-CoV, and MERS-CoV) and recently, the SARS-CoV-2 (2019 novel coronavirus disease (COVID-19)) reported in Wuhan, China in December 2019 (Li *et al*., 2020). Even though SARS-CoV-2 bears similarity with other coronaviruses in clinical manifestation and genome, each strain has distinct additional ORFs (Adhikari *et al*., 2020).

We report the pathogenesis, transmission patterns, and SARS-CoV-2 genome and proteomic features that play a role

as potential drug and vaccine targets. We envisage that this review will provide an insightful overview of the novel virus and assist as a reference in management efforts against the COVID19.

SEARCH METHOD AND SELECTION OF ARTICLES

The literature search was conducted through mainly the PubMed, Web of Science, Science Direct, BMJ, Oxford as well as THE LANCET journals using the following key words: COVID-19, Coronavirus, SARS-CoV-2, SARS-CoV-2 genome and COVID-19 drug discovery in order to retrieve recent articles published on coronavirus pandemic worldwide. In addition, we considered findings obtained through hand searching in WHO reports. After checking the reference list of each study found via the above methods, any old data presenting inappropriate topics which were not in accordance to the purpose of this studies were excluded.

DATA COLLECTION AND ANALYSIS

A total of five review authors were available to screen both the title and abstracts of all the retrieved studies in order to identify and remove studies which do not meet the inclusion criteria. The entire text was read for all retained articles and final agreement was taken for each article. The same five review authors who selected independently the articles extracted also the data using a form containing the study characteristics such as the pathogenesis of SARS-CoV-2, 2019 novel coronavirus, evolution of coronavirus, drug discovery against COVID-19 and proteome and efforts on SARS-CoV-2 vaccine development. For any difference of opinion, all the review authors were consulted and discussed to provide conclusion after completion of data selection.

CURRENT STATUS OF KNOWLEDGE

Severe acute respiratory syndrome coronaviruses (SARS-CoV): Severe acute respiratory syndrome (SARS) caused by novel SARS-associated coronavirus (SARS-CoV) was considered as a natural catastrophe that affected China in the twenty-first century (Peiris *et al.,* 2003). The epidemic features of this disease had initially emerged as human pneumonia- associated disease and were reported for the first time in November 2002 in Southern China, particularly in Guangdong province (WHOa, 2003). Following its introduction in Hong Kong by an infected physician from the mainland in mid-February 2003, the virus has spread quickly to various countries over the world (more than 30 countries) through international air travel involving more than 8000 persons worldwide with 774 deaths reported and a fatality rate of 9.6% (WHOb, 2003). Due to the rapid spread and increase of this uncommon infection, the World Health Organization (WHO) designated this condition severe acute respiratory syndrome" (SARS). Infected patients present main flu-like symptoms such as fever, chills, cough, and malaise. Transmission between humans occurs by direct contact, droplet, as well as airborne routes.

Additionally, the identification of the viral genome in both fecal and urine samples indicated additional routes of transmission. Equally, several animals such as civet cats, raccoon dogs, and different bat species have been identified to be natural reservoirs (Peiris *et al.,* 2003). like the other coronaviruses, the SARS-CoV membrane proteins, including the major proteins S (Spike) and M (membrane), which are placed into Golgi intermediate compartment of the endoplasmic reticulum (ER), while the RNA plus strands assemble with the N (nucleocapsid) protein (Guan *et al.,* 2004). Because of the high prevalence, widespread and distribution of coronaviruses, the high genetic diversity, regular recombination of their genomes as well as human-animal interaction, novel coronaviruses are predicted to emerge occasionally in humans (Cui *et al.,* 2019).

Since December 2019, several local health facilities reported a high number of patients with pneumonia of unknown causative agents in Wuhan, a large city located in central China with about 11 million habitats (WMHC, 2020). A study on the epidemiology and etiology was quickly carried out by the China CDC in Wuhan and reported a respiratory disease spreading from one person to another caused by a novel (new) coronavirus. This report largely advised the decision by the World Health Organization (WHO) on 29 December 2019 to use the term 2019 novel coronavirus to refer to the coronavirus responsible for lower respiratory tract infection in patients in Wuhan. The disease was given the official designation as coronavirus disease (COVID-19) (Li *et al.,* 2020).

The 2019 novel coronavirus (SARS-COV-2): Severe acute respiratory syndrome coronavirus 2 (*SARS-CoV-2*), is the causative agent of coronavirus disease 2019 (*COVID-19*), typical viral pneumonia responsible for the recent unusual outbreak in Wuhan. After the Middle East respiratory syndrome coronavirus (*MERS-CoV*) and severe acute respiratory syndrome coronavirus (*SARS-CoV*) in the twenty-first century, the emergence of SARS-CoV-2 has been marked as the third incidence of a highly pathogenic coronavirus among the human population (Li *et al.,* 2020). The disease has spread quickly and widely since its initial report in Wuhan, China, since December 2019, with a high mortality rate, especially among aged people from above 60 years old (Zhou *et al.,* 2020).

Typically, the clinical and paraclinical signs of COVID-19 in infected patient occurs between the first day of exposure to 14 days post-exposure with the majority of patients presenting symptoms such as high fever, cough, fatigue, difficulty in breathing, irritation of the throat and headache (Guan *et al.,* 2020). Additionally, respiratory symptoms such as high levels of pro-inflammatory cytokines in plasma, as well as higher leukocyte numbers, have been reported (Jin *et al.,* 2020). As a main respiratory system targeting virus, the most pathogenic lesions for COVID-19 infection include severe pneumonia, joined together with the incidence of ground-glass opacities, and acute cardiac injury (Jin *et al.,* 2020). Moreover, few patients fall in critical condition by developing acute respiratory distress syndrome, respiratory failure, multiple organ failure, and deaths (Huang *et al.,* 2020).

SARS-CoV-2 pathogenesis: Several scientists in China and in the world discovered that SARS-CoV-2, just like SARS-CoV, requires the angiotensin-converting enzyme 2 (ACE2). This enzyme plays an important role as a receptor to enter cells

(Zhou *et al.*, 2020). Previously, Raj *et al.* (2013) identified Dipeptidyl peptidase 4 (DPP4, which is also named CD26). This MERS-CoV functional receptor from spike protein was purified with DPP4 from susceptible cells of Huh-7 lysates. This protein (MERS-CoV) can attach to DPP4 from several species, including humans. This explains and promotes the theory of transmission to humans and other species, and infection of cells from a large number of species (Barlan *et al.*, 2014).

The similarity of SARS-CoV and MERS-CoV pathogenesis can be inferred to SARS-CoV-2 to recognize COVID-19, as its pathogenesis is still under investigation and remains poorly understood to date. On approximately 30% of the genome, four structural proteins are encoded. These proteins included: envelope protein (E), spike protein (S), membrane protein (M), and nucleocapsid protein (N) as well as several accessory proteins with unknown functions. For most coronaviruses, the corresponding receptors on target cells are mainly recognized through S proteins on their surface (Fig. 1).

The first step in infection is the entry of the virus into the host cells (Wang *et al.*, 2020). The SARS-CoV-2 entry into the cell of the host is facilitated by envelope spike glycoprotein (S), which binds by membrane fusion to the plasma membrane and the virus via the receptor ACE2 and CD209L (a lectin named L-SIGN) (Wu *et al.*, 2020). The virus might enter through the mucous membranes, particularly nasal and larynx mucosa, then passes to the lungs through the respiratory tract (Lu *et al.*, 2020). Target organs that express ACE2, such as the lungs, heart, renal system, and gastrointestinal tract, will be affected by the virus. The second step in the infection attack starts by changing patient's state to worsen about 7 to 14 days after onset (Adhikari *et al.*, 2020). For the mechanism of COVID-19 treatment and prevention, it is important to understand the virus pathogenicity (Li *et al.*, 2020). When the virus enters the cells via the MHC I molecules and sometimes MHC II, the antigen presentation cells (APC) are activated (Fig. 1).

Genetic structure of SARS-CoV-2 genome: SARS-CoV-2 genome has six major open-reading frames (ORFs) that are common to coronaviruses. In addition to these ORFs, SARS-CoV-2 encodes accessory genes in four more ORFs bringing a total to at least ten ORFs (Fig. 2). The first open reading frame (ORF1a/b), which covered approximatively two-thirds of the RNA is translated into 2 big proteins. The complex of viral replicase transcriptase is formed by the PP1a and PP1ab polyproteins of MERS-CoV and SARS-CoV that are processed into sixteen nonstructural proteins (nsp1-nsp16) (Zhang, 2020).

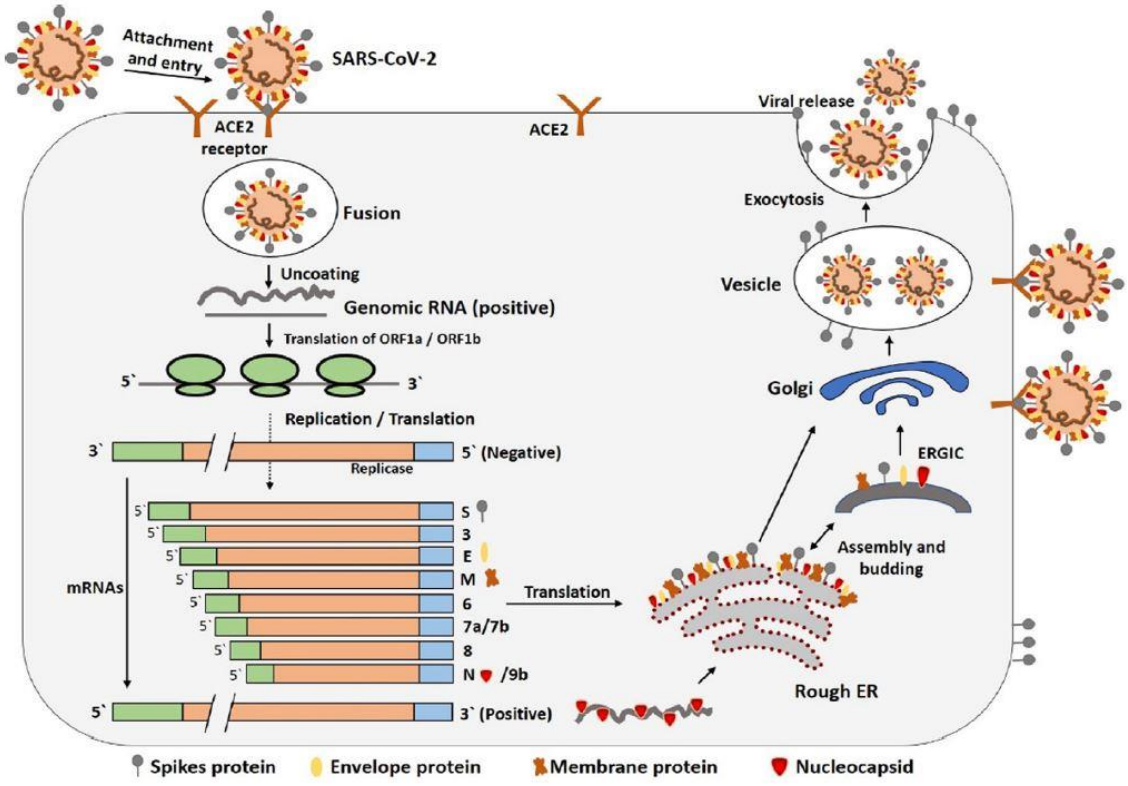

Figure 1

The life cycle of SARS-CoV-2in human lung cells. Transmission of the virus is by droplets during sneezing and coughing followed by infiltration to the upper respiratory tract. S-glycoprotein binds to human ACE2 receptors, the fusion of viral and host's membrane occurs and the viral RNA is released into the cell cytoplasm. Transcription and translation of the viral RNA begins and finally, the assembly and release of infectious viral particles through exocytosis mark the end of the cycle. (Adnan *et al*., 2020).

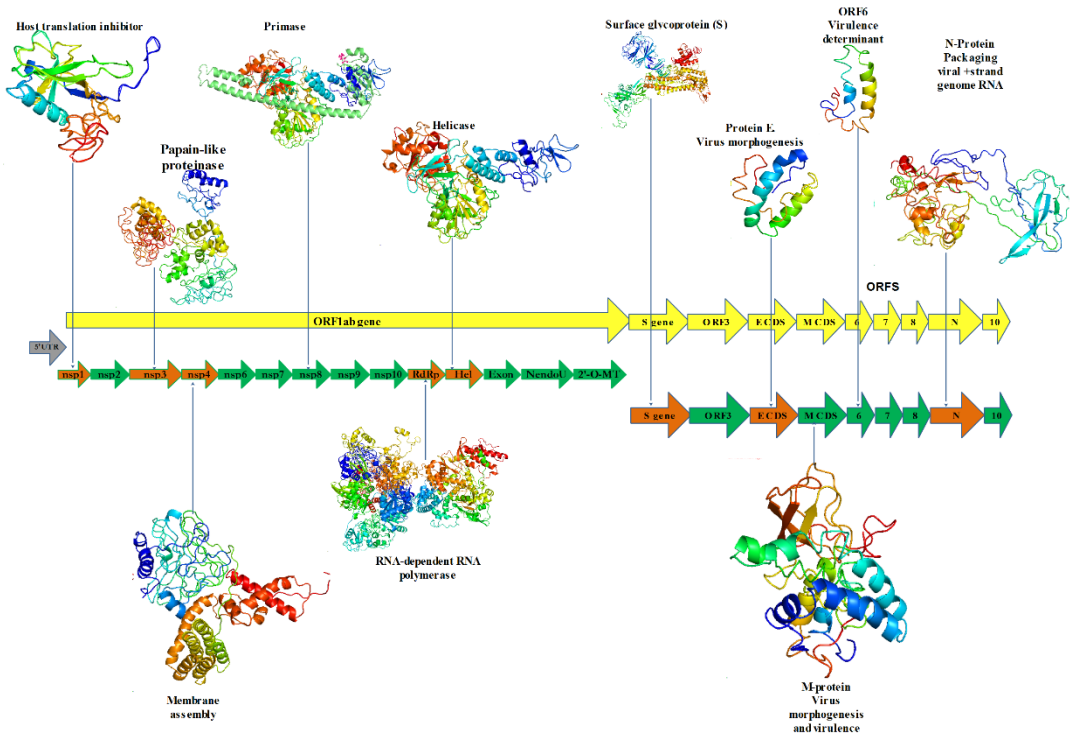

Figure 2:
The genome structure and encoded proteins of SARS coronavirus 2. The yellow tracks represent the genes (CDSs) while the lower track (green and brown) represents individual protein-coding domains. Highlighted (in brown) proteins play major roles in viral replication, assembly, virulence, and morphogenesis. (Zhang Yang Lab, 2020).

The rough endoplasmic reticulum is the origin of these nonstructural proteins rearrange membranes. The transcription and replication of the SARS virus occur in double-membrane vesicles (DeLano, 2020). Recently some studies showed that the SARS-CoV nucleotide sequences share less than 80% identity with other 2019-nCoV genomes (Li *et al.*, 2020; Zhou *et al.*, 2020). However, the protein sequencing of seven conserved regions in the open reading frame 1ab used the classification and similarities of coronaviruses showed 94.4% of identity between SARS-CoV and the novel 2019-nCoV. This high similarity showed that these two viruses belong to the same SARSr-CoV species (Raj *et al.*, 2013).

Among all studied RNA viruses, CoV has the longest genome with about 32 to 43% of GC contents with several small open reading frames within and between conserved regions in various genes and downstream to the nucleocapsid protein in many lineages of coronavirus. Genes for the major structural proteins in all coronaviruses occur in the '5'-'3'order direction (Su *et al.*, 2016). The '5'UTR and '3'UTR are involved in inter-and intramolecular interactions. This region plays a major role in RNA-RNA interactions and cellular proteins and virus binding.

The length of the encoded proteins are 29844bp (7096aa) for COVID-19, 29751bp (7073aa) for SARS-CoV, and 30119bp (7078) for MERS-CoV at the 5' end in the first open reading frame (ORF-Pb1ab) of the genome. From a recent comparative genomic study, the visualized difference was 1273aa for COVID-19, 21493aa for SARS-CoV, and 1270aa in MERS-CoV when the spike protein compared among the tree beta coronaviruses. Indeeed, the SARS-CoV-2 genome was 79% similar to SARS-CoV and 50% similar to MERS-CoV. The arrangement of nucleocapsid protein (N), an envelope protein (E), and membrane protein (M) among beta coronaviruses is different (Mousavizadeh and Ghasemi, 2010).

Evolution of coronavirus: The novel coronavirus (SARS-Cov2) clusters in Sarbecovirus subgenus, Beta coronavirus genus and family Coronavirus. The origin of SARS-Cov2 is yet to be conclusively defined even though several studies have reported a close similarity to coronaviruses derived from bats (Li *et al.*, 2020; Vijaykrishna *et al.*, 2007). The majority of studies, are arriving at the same conclusion on the possibility of interspecies transmission of coronaviruses.

Recently, Li *et al.*, (2020) identified coronaviruses strains from five wild animals that share a close nucleotide sequence similarity with the novel coronavirus. For phylogeny, to infer the genetic relationship between different coronavirus isolates, we aligned a total of 27-genomic sequences of coronaviruses from different regions retrieved from the GenBank database. All isolates from fifteen random representative samples collected in 2020 from different regions clustered in a single clade.

Our phylogenetic tree showed a close evolutionary relationship to coronaviruses derived from bats, and an even closer relationship to pangolin coronaviruses (Fig. 3). Besides this being in agreement with Zhang *et al.*, (2020) on the

observed closer relationship between spike protein amino acid sequences from SARS-COV-2 and pangolin coronavirus compared to bats, it is interesting to note that previous SARS coronaviruses derived from human are clustering way distant from the novel SARS-COV-2. Another notable observation is in the bat coronaviruses evolution, where previous isolates do not fall under the same clade as the recent (2020) isolates and are clustering further away from the novel SARS-COV-2.

PROGRESS IN DRUG DISCOVERY AGAINST COVID-19 PROTEOME:

Viral proteins are important components in drug development pipelines. They can be the main drug targets or modulators of the drug targets and their activities. To this end, up to nine antiviral drugs, including Remdesivir, favipiravir, tocilizumab, camostat mesylate, hydroxychloroquine, ritonavir, and lopinavir are in drug pipelines as the world race against the novel coronavirus (Wu *et al.*, 2020; Arya *et al.*, 2020). The sad tale is that no single drug has been identified so far to effectively work against the virus, with the current treatment strategy being the management of associated COVID symptoms. For this review, we compile reports on the efforts and status of drugs targeting these proteins.

Nonstructural protein1: Towards the '5'UTR end of the genome (Fig. 2) is a region that encodes a 35kDa, nonstructural protein1 (nsp1) common among alphacoronaviruses and beta coronaviruses plays a role in inhibition the host translation through interaction with the small ribosome subunit (Shen *et al.*, 2019). Mutagenesis studies have shown that this interaction leads to the formation of a 40S ribosome-nsp1 complex, which aids in the degradation of host mRNA through endonucleolytic cleavage close to '5'UTR region of the untranslated capped transcript (Ahmed *et al.*, 2020; Kamitani *et al.*, 2009) The viral mRNA is guarded against this endonucleolytic degradation as they possess a 5′-end leader sequence that serves as protection (Subissi *et al.*, 2014). Experimental evidence also points to the role of this protein in inhibition of the beta interferon (β-IFN) expression and suppression of the host innate immune activities (Narayanan *et al.*, 2008).

In pigs, nsp1 from transmissible gastroenteritis virus (TGEV), a member of coronavirus family was reported as an essential virulence determinant, and due to a conserved motif consisting of up to 95 amino acids, this protein has been identified as a potential drug target (Shen *et al.*, 2019). The SARs attenuated recombinant coronavirus vaccine with a deletion of nsp1 homolog in mouse hepatitis virus (MHV) have so far been tested and have shown the ability to induce cytotoxic T cell responses at a low dose (Züst *et al.*, 2007). Equally, drugs that are conventionally used for bacterial therapies including tetracycline, piperacillin, streptomycin, cefpiramide, lymecycline, platycodin D have been shown to strongly bind to Nsp1, Nsp3c, and ORF7a (Wu *et al.*, 2020). Unlike nsp1, whose role is profound, nonstructural protein2 (nsp2) is only involved in the modulation of host cell survival pathways.

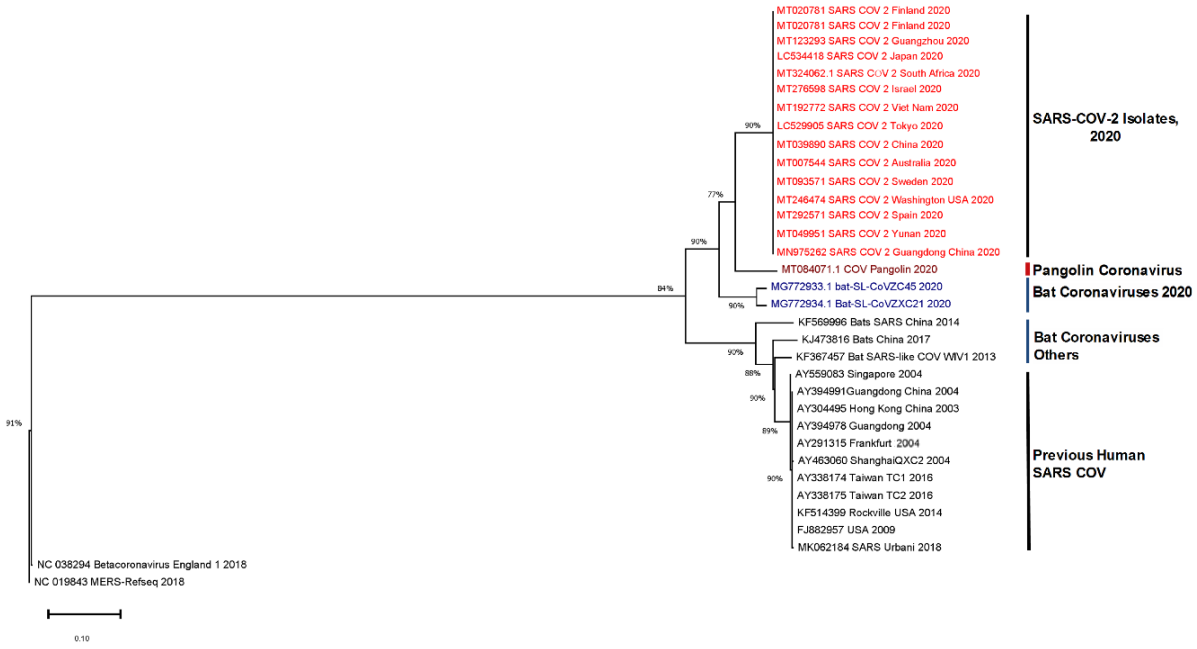

Figure 3:

The phylogenetic relationship among SARS-CoV-2 and other coronaviruses in pangolin, bats, and humans. Red-colored labels represent fifteen (15) different 2020 isolates of SARS-COV-2. Blue and brown coded labels denote coronaviruses from bats and pangolins respectively, the closest relatives to SARS_COV-2. Middle East respiratory syndrome coronavirus (MERS-CoV) Refseq (NC_019843) was used as outgroup. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1000 replicates) are shown next to the branches. The MP tree was obtained using the Subtree-Pruning-Regrafting (SPR) algorithm with search level 1 in which the initial trees were obtained by the random addition of sequences (10 replicates). Evolutionary comparisons were contacted using MEGAX. (Li *et al.*, 2020).

Papain-like proteinase (PLpro): Also called nsp3 is associated with the cleavage activity of the "replicase" n-terminal (Xiao *et al.,* 2012). Nsp3, together with 3C-like protease, is responsible for the replication of genomic RNA. The activity of nsp3 is attributed to the presence of a 316 amino acid catalytic triad domain consisting of cysteine, histidine, and aspartic acid residues (Lindner *et al.,* 2005). Recognition of the substrate by nsp3 is guided by the presence of a recognition site made up of LXGG or its homolog LRGG site (Lindner *et al.,* 2005). Just like nsp1, nsp3 suppresses host immunity by indirectly impeding the induction of type I interferon (IFN) through inhibition of IRF3 phosphorylation (Matthews, 2014). IFN3 is a regulator of cellular responses and an essential component for innate immunity. The inhibition IFN3 is linked to the de-ubiquitination (DUB) activity of nsp3 which suggests this as one of the mechanisms by which the virus modulates the host cellular activities (Lindner *et al.,* 2005; Ratia *et al.,* 2008).

Due to the indispensable roles played by PLpro, several efforts have been made to target this protein. Ratia *et al.,* (2008) screened up to 50000 compounds against PLpro in Vero E6 cells and identified a compound (GRL0617) with the ability to inhibit the protein by binding within the S4-S3 subsites of the nsp3 and inducing a loop closure that halts its catalysis without any cytotoxicity. Equally, in silico docking study by Arya *et al.,* (2020) revealed sixteen FDA approved drugs, including formoterol (a bronchodilator) and chloroquine (a conventional malaria drug) that were able to dock nsp3. Equally, computational analysis of existing antiviral regimens such as thymidine and ribavirin, natural phytochemicals including epigallectin, tanshinones, diarylheptanoids, geranylated flavonoids as well as antibacterial compounds (chloramphenicol and cefamandole) have shown a high binding affinity to PLpro (Wu *et al.,* 2020).

Viral 3-chymotrypsin-like cysteine protease ($3CL^{PRO}$): $3CL^{PRO}$, an approximately 33.1kDa protease, is involved in the control of activities under the virus replication complex. The protein works in tandem with PLpro in cleavage of the C-terminus of replicase polyprotein at 11 sites through their catalytic site, which is defined by the presence of His41 and Cys145 (Wu *et al.,* 2020). Besides the role in processing the viral polyprotein, PLpro has also been associated with shedding ubiquitin and Interferon-stimulated gene 15 (ISG15) from host-cell proteins. This allows the viruses to evade the host innate immune responses (Narayanan *et al.,* 2008). As a drug target, $3CL^{PRO}$ offers more advantages than the other viral proteins in that inhibiting it not only disrupts the replication ability of the virus but also sensitizes it to the host immunity. In a study to identify the potential active site of this protein, Bacha *et al.,* (2004) discovered the presence of subsites containing serine residues at positions 139, 144, and 147 that can be targeted by boronic acid-containing compounds. This observation on the ability of a boron-containing compound to inhibit proteases is also supported by Soriano-Ursua, (2020) findings on inhibition of SARS-CoV-2 main protease.

RNA-dependent RNA polymerase (RdRp): RdRp, a non-structural protein encoded at position 12 (nsp12) of the pab1 polyprotein, is among the essential protease in coronaviruses and act as a core enzyme in both replication and translation of the viral genetic material (Zumla, 2016). Unlike other viruses, coronavirus encodes a proofreading mechanism in nsp14 protein, which aids the RdRp in conferring a relatively higher fidelity replication compared to other viruses. The requisite role of RdRp in replication of the viral RNA genome makes it a desirable candidate for the development of coronavirus drugs. Indeed, several drugs are in the trial stage against RdRp in coronaviruses. Among these drugs is Remdesivir (RDV), a nucleotide analog inhibitor of RdRp, which has a broad spectrum of antiviral activities against several RNA viruses (Gordon *et al.,* 2020). Even though this is not yet proven experimentally, it is proposed that the RDV competes with ATP by binding to the region of the protein leading to the arrest of RNA synthesis and, subsequently, delayed transcript (mRNA) chain termination. A culture-based experiment on the effects of aurintricarboxylic acid (ATA) on the replication of SARS-CoV demonstrated a significantly reduced viral mRNA (up to 1000-fold less) for cells treated with ATA. A comparison of this drug potency to interferons demonstrated a 10fold higher performance (He *et al.,* 2004).

Spike protein(S): Following the Polyprotein ab1 is the spike glycoprotein(S), also called surface glycoprotein whose role is in interaction with the host ACE-2 receptors during infection and acts as the basic necessity for the entry of coronavirus into the host cell (Zumla *et al.,* 2009). Studies in murine coronavirus mouse hepatitis virus revealed the size of this protein to be approximately 180kDa and are cleaved post-translationally into S1 and S2 proteins. Binding of the virus to the host receptor is achieved through the S1 subunit, while S2 is believed to contain internal fusion peptides that are involved in the fusion of the viral and host membranes. As a drug target, antiviral drugs against other enveloped viruses such as the hepatitis C virus were shown by computational methods as potent inhibitors for S-proteins (M.S.H.J.G.T.E, 2020). These drugs include paritaprevir, grazoprevir, velpatasvir, and simeprevir.

The bottom line on the applicability of SARS-CoV-2 proteins as drug targets: Viruses are prone to mutations, and this is expected for coronaviruses with a more accelerated evolutionary rate as they are single-stranded RNA viruses. Efforts in developing drugs targeting such viruses or their proteins often end up becoming futile despite the promising potential. With this in mind, we aligned the amino acid sequences of the reviewed proteins from three different, random isolates of SARS-CoV-2 collected in different timespan as well as two viruses belonging to coronavirus family to test their similarity. From the alignment, it is clear that the amino acid residues for these proteins are relatively conserved within the SARs human isolates and Bat SARs coronavirus (Fig. 4). This is, however, not true for the Middle East respiratory syndrome coronavirus (MERS-CoV) where clear differences from other coronaviruses can be seen. With this evidence, spike, 3CLpro, envelope, and PLpro can serve as useful candidates for the development of drugs/inhibitors against SARS coronavirus.

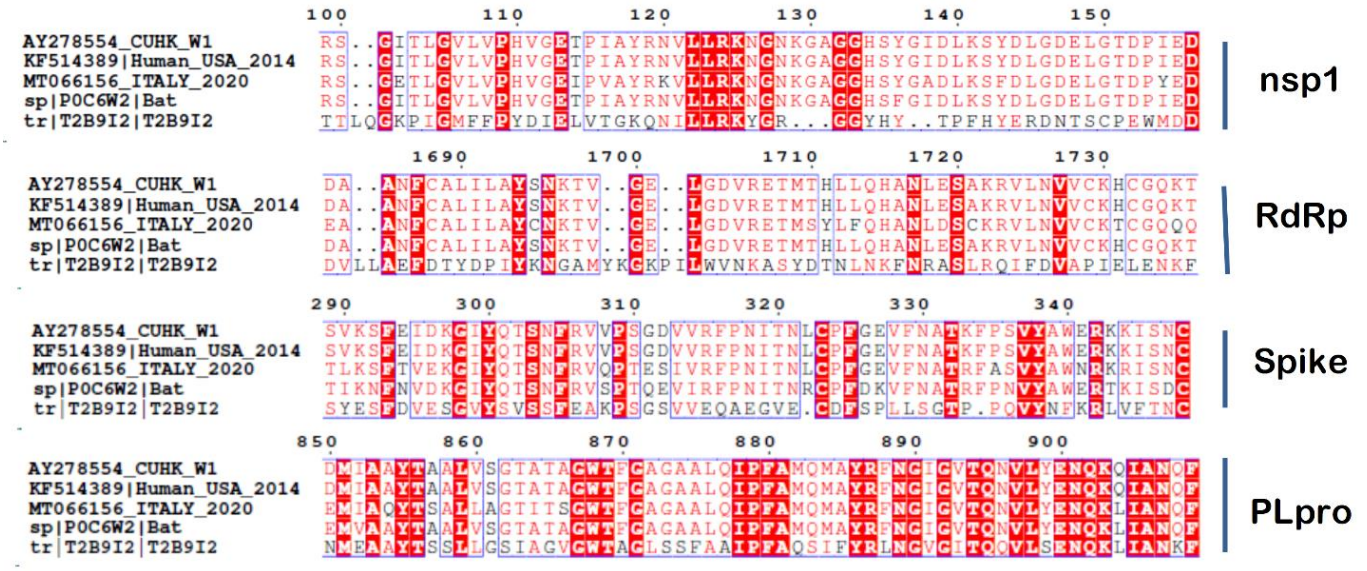

Figure 4:
A snapshot of amino acids alignment of six different isolates including Wuhan 2020 or SARS-CoV-2 (AY278554), USA 2014 or SARS-CoV-2 (KF514389), Italy 2020 or SARS-CoV-2 (MT066156), Bat coronavirus 2013 (PDB: P0C6W2), and MERS coronavirus 2020 (PDB: T2B9I2). The left panel shows the accession of the strains used for this comparison. For the aligned proteins, PLpro, Spike, RdRp and nsp1, negligible differences in amino acid sequences is clear between the isolates with an exception of MERS. (Wu *et al*., 2020).

Prospect of developing a SARS vaccine: The progress that is perhaps being closely monitored is the development of a COVID-19 vaccine. Designing a safe vaccine for a new illness is no easy feat. Thankfully, rapid progress is being made for a variety of reasons, including China's efforts in sequencing Sars-CoV-2 genome and global sharing of information among the research groups. SARS and MERS' etiological agents are coronaviruses and even though vaccines were shelved once previous outbreaks were contained, lessons can still be drawn from them. Despite the several efforts made to contain CoV infections, the extensive sequence diversity (Graham *et al.*, 2013) of the causative agents renders them futile. It is however encouraging that most of the previous therapeutic options that are promising in the management of COVID-19 are based on previous experiences in treating SARS- and MERS-CoV (Kuldeep, 2020).

The use of next-generation sequencing and reverse genetics may also reduce the development time of more conventional vaccines during epidemics. A more complete and continually updated list is available from the World Health Organization (WHOc, 2020). First, although the virus's spike protein is a promising immunogen for protection, optimizing antigen design is critical to ensure optimal immune response. Debate continues over the best approach for example, targeting the full-length protein or only the receptor-binding domain. Second, preclinical experience with vaccine candidates for SARS and the Middle East respiratory syndrome (MERS) has raised concerns about exacerbating lung disease, either directly or as a result of antibody-dependent enhancement. Such an adverse effect may be associated with a type 2 helper T-cell (Th2) response (Chen *et al.*, 2020).

Multiple strategies are adopted in the development of CoV vaccines; most of this target the surface-exposed spike (S) glycoprotein or S protein as the major inducer of neutralizing antibodies. Several S-protein-based strategies have been attempted for developing CoV vaccines, e.g., use of full-length S protein or S1receptor-binding domain (RBD) and expression in virus-like particles (VLP), DNA, or viral vectors with the S protein molecule containing two subunits, S1 and S2 (Graham *et al.*, 2013). The first subunit has an RBD that interacts with its host cell receptor, angiotensin-converting enzyme 2 (ACE2), whereas the S2 subunit mediates fusion between the virus and host cell membranes for releasing viral RNA into the cytoplasm for replication. It has been shown that the C-terminal domain of the S1 subunit of porcine Delta coronavirus constitutes the immunodominant region, and the immune response to this region shows the most potent neutralizing effect (Chen *et al.*, 2020). Despite the high genetic similarity between SARS-CoV-2 and SARS-CoV, the possibility of developing a universal CoV vaccine was performed and assessed based on the similarity in T-cell epitopes of SARS and MERS-CoV that confirmed the potential for cross-reactivity among CoVs. Thus vaccines developed for SARS-CoV may probably exhibit cross-reactivity to SARS-CoV-2.The comparative evaluation performed on full-length S protein sequences of SARS-CoV-2 and SARS-CoV identified that the most variable residues were located in the S1 subunit of S protein, the critical CoV vaccine target (Li *et al.*, 2020; Chen *et al.*, 2020). The NIAID-VRC scientists are developing a vaccine candidate expressing SARS-CoV-2 S protein in the mRNA vaccine platform technology.

Future prospects: Achievements in the development of vaccines and therapeutic agents for SARS- and MERS-CoV, as well as ongoing progress for COVID-19, will facilitate the development of effective vaccines and therapeutics against this emerging virus (Hopman, 2020). However, the present scenario of COVID-19 warrants the need for implementing robust preventive and control measures due to the potential for nosocomial infections. Results obtained from the recently conducted in vitro study against COVID-19 are promising since the drugs remdesivir and chloroquine were found to be highly effective in controlling the infection (El Bcheraoui *et al.,* 2020). Although research is in progress to improve prevention, treatment, and control of COVID-19, the documented clinical data on different therapeutic approaches for CoVs are scarce. Further research should be directed toward the study of SARS-CoV-2 in suitable animal models for analyzing replication, transmission, and pathogenesis (Chin *et al.,* 2020). The assessment of health and socio-economic impacts of this pandemic.

CONCLUSION

The coronavirus disease 19 (COVID-19) is a highly contagious and lethal viral disease caused by SARS-CoV-2 and originated from Wuhan, China which has spread over the world. Genetic analysis showed that SARS-CoV-2 is genetically related to severe acute respiratory syndrome-like (SARS-like) bat viruses suggesting that bats could be potential primary reservoir. To date, no effective treatment or prevention is available against human coronaviruses. However, research are ongoing to develop efficient preventive and therapeutic measures to get through with the novel coronaviruses. Nevertheless, little clinical trials on antiviral drugs against COVI-19 have been performed and resulted in some clinical recoveries. In addition, there are currently several companies working for the development of efficient SARS-CoV-2 vaccines bust still will undergo human and animal-based trails before commercialization. Efforts on targeting vaccines and antiviral drugs for human coronavirus are still needed that could be used for the current and future epidemics.

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