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Molecular Basis of Pathogenesis of Coronaviruses: A Comparative Genomics Approach to Planetary Health to Prevent Zoonotic Outbreaks in the 21st Century

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Abstract

In the first quarter of the 21st century, we are already facing the third emergence of a coronavirus outbreak, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for the coronavirus disease 2019 (COVID-19) pandemic. Comparative genomics can inform a deeper understanding of the pathogenesis of COVID-19. Previous strains of coronavirus, SARS-CoV, and Middle-East respiratory syndrome-coronavirus (MERS-CoV), have been known to cause acute lung injuries in humans. SARS-CoV-2 shares genetic similarity with SARS-CoV with some modification in the S protein leading to their enhanced binding affinity toward the angiotensin-converting enzyme 2 (ACE2) receptors of human lung cells. This expert review examines the features of all three coronaviruses through a conceptual lens of comparative genomics. In particular, the life cycle of SARS-CoV-2 that enables its survival within the host is highlighted. Susceptibility of humans to coronavirus outbreaks in the 21st century calls for comparisons of the transmission history, hosts, reservoirs, and fatality rates of these viruses so that evidence-based and effective planetary health interventions can be devised to prevent future zoonotic outbreaks. Comparative genomics offers new insights on putative and novel viral targets with an eye to both therapeutic innovation and prevention. We conclude the expert review by (1) articulating the lessons learned so far, whereas the research is still being actively sought after in the field, and (2) the challenges and prospects in deciphering the linkages among multiomics biological variability and COVID-19 pathogenesis.

Keywords: SARS-CoV-2, COVID-19, SARS-CoV, MERS-CoV, comparative genomics, planetary health

Introduction

Microorganisms (bacteria, viruses, and their products) have well-known potential to cause diseases in plants and animals, including humans (Atlas, 2002). Historically, epidemics and pandemics are informative accounts emphasizing the ability of microbes in causing a risk to the lives of mankind (Thavaselvam and Vijayaraghavan, 2010). Through intentional use as biological agents, mishandling, or by unchecked consumption and dietary habits of human populations, microbial agents have become powerful in causing infections and killing millions of people around the world (Hays, 2005; Thavaselvam and Vijayaraghavan, 2010). The world is now facing a similar situation where novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) has taken the lives of many people by coronavirus disease 2019 (COVID-19) (Lai et al., 2020).

Several diagnostic and therapeutic approaches are in a trial to control the COVID-19 (Kumari et al., 2020; Mohammad et al., 2020; Shamsi et al., 2020). However, a comprehensive understanding of molecular basis of pathogenicity of SARS-CoV-2 is still needed (Iyer et al., 2020). To this end, comparative genomics can inform a deeper understanding of the pathogenesis of COVID-19.

Coronaviruses (CoVs) are single-stranded RNA (ssRNA) enveloped viruses belonging to the Coronaviridae family. It has derived its name because of its spikes having a crown-like appearance on the outer surface. The viruses are extremely

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small (65–125 nm in diameter) in size ranging from 26 to 32 kb in length (Cao et al., 2020; Shereen et al., 2020). Several strains of CoVs in the past such as SARS-CoV, Middle-East respiratory syndrome-coronavirus (MERS-CoV), and recently a new strain, SARS-CoV-2, are associated with outbreaks of respiratory and systemic illness (Cui et al., 2019). All three viruses belong to the beta (β) subgroup of CoVs (Pyrc et al., 2007). Figure 1 shows the timelines of all the three zoonotic outbreaks that have occurred with CoVs.

Originally, the basis of transmission of CoVs was restricted to animals until the first case of SARS-CoV transmission into humans happened in 2003 (Peiris et al., 2004). The patients showed symptoms of pneumonia leading to alveolar injuries finally causing acute respiratory distress syndrome. Then, a decade later in 2012, MERS-CoV started to emerge from the Arabian peninsula through coming in direct and indirect contact with camels (Rahman and Sarkar, 2019). It caused severe pneumonia in humans and clinical symptoms were similar to acute respiratory syndrome (Wang et al., 2013).

Renal failure was found to be the main reason for mortality after the viral attack (Memish et al., 2013). The SARS-CoV-2 is first identified in December 2019 at Wuhan, China, causing the COVID-19 pandemic as declared by the World Health Organization (WHO) (Cui et al., 2019). Until August 2020, the disease spread to 213 countries and territories and two international conveyances with >25 million confirmed cases and around 0.85 million deaths across the world. (https://www.worldometers.info/coronavirus/). Its fast transmission rate has brought an economic and social burden to people and the countries affected by this outbreak.

The lack of vaccines and therapeutic drugs makes it important to compare the SARS-CoV-2 with previous strains of CoV (MERS-CoV vs. SARS-CoV vs. SARS-CoV-2) to obtain new insights crucial for understanding the viral targets. Genetic studies have been successfully used to the sequence maps about variations on a genomic level in the past (Knoppers and Chadwick, 2005). The characteristics, functionality, and structure are largely dependent upon the nature of the genes residing in the organism's genome. Therefore, the reason behind the varied transmission, pathogenicity, and fatality rates exhibited by three CoVs (SARS-CoV vs. MERS-CoV vs. SARS-CoV-2) may be obtained by having a closer look into the multiomics biological features of each discussed CoV strain.

Table 1 provides an overall comparison of CoVs in terms of their origin, fatality rate, transmission rate, hosts and reservoirs, and other quantitative metrics, including basic reproduction rate (R_0) value and known risk factors.

In this expert review, we examined the comparative genomics-based analyses on genetic modifications of SARS-CoV-2 and other virus characteristics in relation to the past viral strains of CoVs. Different multiomic strategies in studying the COVID-19 characteristics are also discussed in this article.

The Genetic Makeup of Coronaviruses

CoVs are positive-sense ssRNA viruses that are enveloped in nature having a comparatively larger genome size ($\sim$30 kb) (Naqvi et al., 2020; Zhang and Holmes, 2020). A typical structure of CoV possesses nonstructural proteins (nsp); structural proteins such as spike (S), envelope (E) membrane (M), and nucleocapsid (N), and accessory proteins are illustrated in Figure 2.

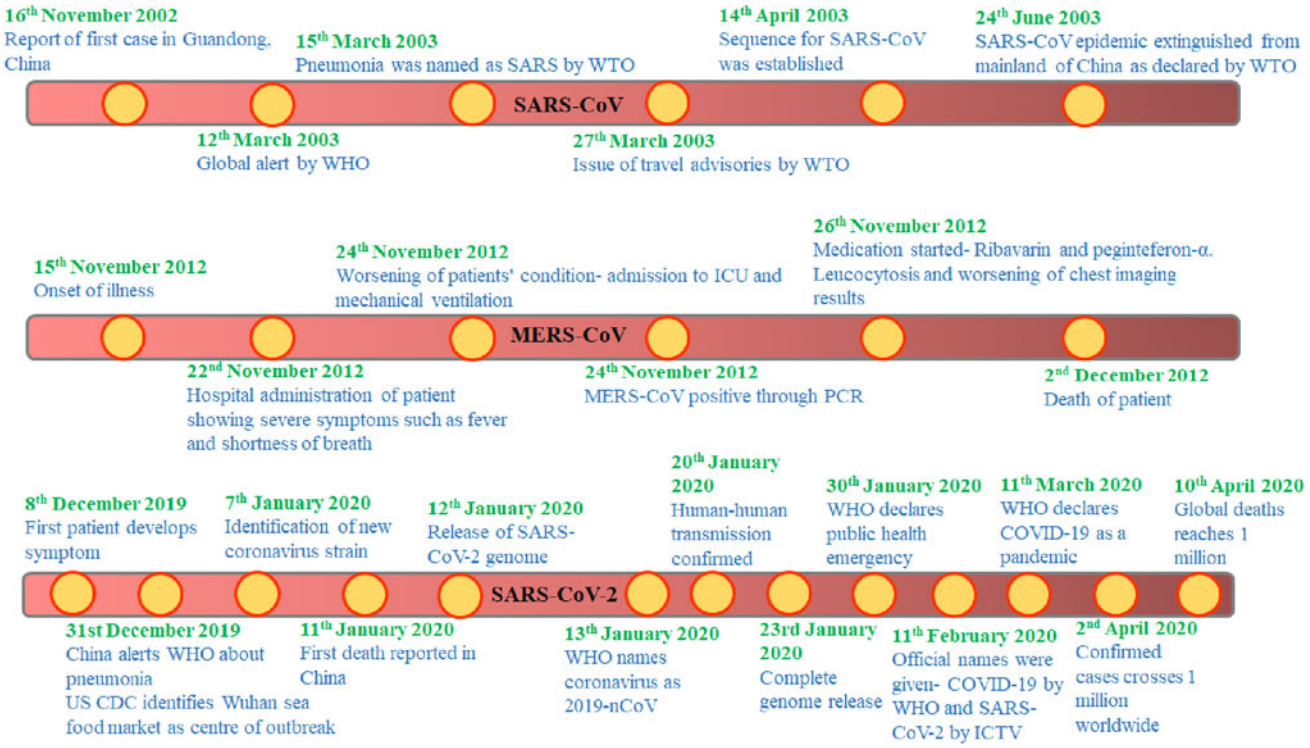

FIG. 1. Timeline of outbreaks of three main coronaviruses.

Table 1. Characteristics and Pathogenesis of Coronaviruses Outbreaks

Characteristics	*SARS-CoV*	*MERS-CoV*	*SARS-CoV-2*
Origin of infection	Guangdong in China, 2003	Saudi Arabia, 2012	Wuhan in China, 2019
Hosts	Chinese Horseshoe bats	Pipistrellus and Perimyotis bats	Bats
Reservoir/intermediary host	Himalayan palm civet	Dromedary camels	Pangolins
Total number of infections	>8000	2428	23 million and evolving
Total number of deaths	776	838	0.82 million (as of 26th August 2020)
Fatality rate	>10%	35%	1–4%
Transmission region	Globally	Regionally	Globally
Basic reproduction number (R_0)	3	<1	2–2.5
Receptor	ACE2*	DPP4*	ACE2*
Viral replication efficiency	High	Higher	Highest
Examples of risk factors	Health care procedures generating aerosols, increasing age, male sex, presence of comorbidities, slaughter of wildlife for human consumption	Exposure to camels, people with diabetes; kidney failure; heart disease; chronic lung disease or weakened immune system	Increasing age, people with existing medical conditions such as obesity, heart disease, type-2 diabetes mellitus, pulmonary obstructive lung disease, sickle cell, cancer, and immunocompromised individuals are at higher risk
Cell line susceptibility	Respiratory tract; kidney and liver	Respiratory tract; urinary tract; liver, kidney, gastrointestinal tract; and neurons	Respiratory tract; kidney and liver, others are being deciphered currently

References as cited within the text.
*ACE2 is a cellular receptor for SARS-CoV and SARS-CoV-2. DPP4 is a cellular receptor for MERS-CoV. In MERS-CoV infection, DPP4 is not involved in cleaving of various cytokines in the airways and thus contributes in lung inflammation.
ACE2, angiotensin-converting enzyme 2; DPP4, dipeptidyl peptidase 4.

The four structural proteins contribute to the development of viral structural features as their name suggests. Spike protein mediates the attachment of the virus to the host receptors leading to their fusion with the cell membrane (Kandeel et al., 2018; Siddell, 1995). N-protein synthesizes nucleocapsid of the virus by interacting with the viral mRNA for the formation of ribonucleoprotein (Risco et al., 1996). E-protein forms viral envelope assembling virions (Ruch and Machamer, 2012), whereas M protein synthesizes the viral membrane for assembly of mature virus particles (Neuman et al., 2011).

A general order of arrangement of the genome is as follows: [5′ replicase (rep gene), spike (S), envelope (E), membrane (M), and nucleocapsid (N), accessory genes 3′] (Song et al., 2019). Replicase genes synthesize nsp required for replication of the virus. Accessory proteins may differ in other strains of CoVs. These genetic changes in the accessory proteins might be responsible for the greater pathogenicity of

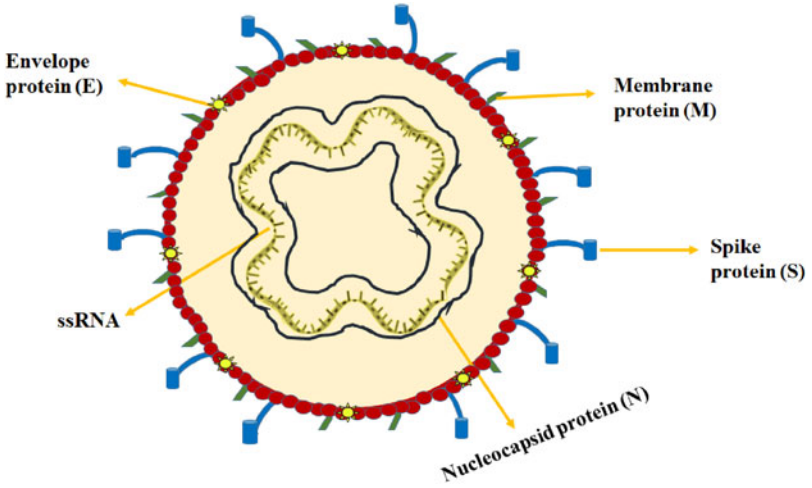

FIG. 2. Structural representation of coronavirus. The figure shows four structural proteins, spike protein (S), membrane protein (M), an envelope protein (E), and nucleocapsid protein (N) of coronaviruses.

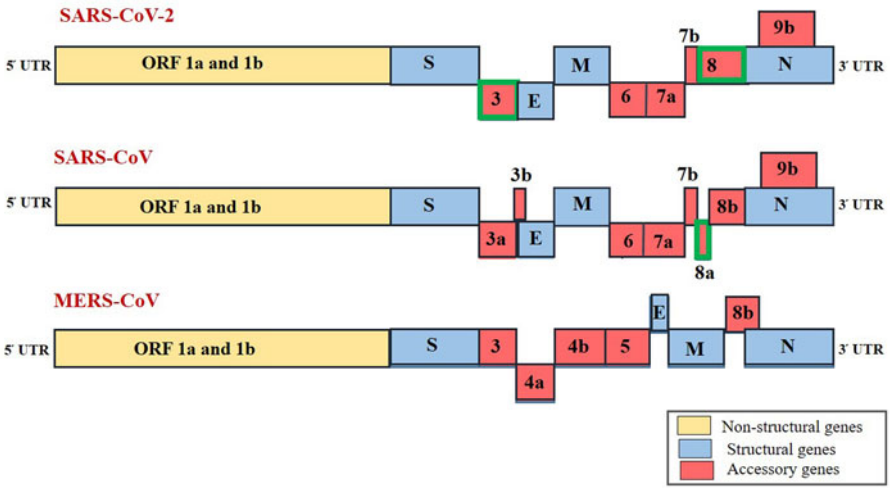

FIG. 3. Genome structure of coronaviruses. A typical gene structure of coronaviruses contains [5′ UTR; ORF 1a and 1b (rep gene); S, E, M, N, and accessory genes; 3′UTR]. Accessory genes differ among the three compared CoVs. More similarities occur between SARS-CoV and SARS-CoV-2; however, *green bold boxes* indicate differences in accessory genes present in their genetic material. ORF, open reading frame; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

certain CoVs then their other counterparts (Li et al., 2020a). A detailed genomic description of each of the CoV is discussed as follows.

The genome of SARS-CoV contains about 29,727 nucleotides, including 11 open reading frames (ORFs) that are functional (Rota et al., 2003). Two ORFs are found between S and E genes, whereas 5 ORFs are found between M and N genes (Satija and Lal, 2007). ORF1 is responsible for viral replication, spike, and nucleocapsid formation (van Boheemen et al., 2012). The structural arrangement suggested the presence of genes 1a and 1b (polyprotein AB in case of MERS-CoV), four structural genes; and five accessory genes in 5′–3′ direction. This gene 1a and 1b undergo proteolysis for the synthesis of nsp (Song et al., 2019).

MERS-CoV genome evolved through various mechanisms and proved to be more infective than its earlier counterpart, SARS-CoV (Naqvi et al., 2020; Yin and Wunderink, 2018). This viral strain has 30,119 nucleotides and is larger. It consists of 5′ cap and 3′ poly (A) tail at its terminal ends. 5′ end constitutes *rep* gene required for the synthesis of 16 nsp (nsp 1–16). These proteins are in the form of polyprotein AB, which is cleaved further by papain-like proteases for nsp production. The 3′ terminus end of this virus is marked with the presence of four structural genes (S, M, E, and N) and five accessory genes, including ORF3, ORF4a, ORF4b, ORF5, and ORF8. The accessory proteins were found to play an important role in invading the immune system of the host specifically targeting the innate immune responses.

Close inspection of the genome during the viral outbreak revealed the high possibilities of genetic recombination in the MERS-CoV genome (Zaki et al., 2012). Thus, higher sensitivities toward induction and signaling mechanisms of type 1 interferons were attributed to MERS-CoV then SARS-CoV, proving to be more fatal (Song et al., 2019).

SARS-CoV-2 possesses structural features similar to the typical CoVs, but certain genomic variations are observed in this novel strain (Fig. 3). Almost 80% of the genomes resemble one another, whereas the most closely related to this is SARS-CoV as indicated in the phylogenetic trees by several research studies (Liang et al., 2020). A typical SARS-CoV-2 genomic structure comprises 5′ untranslated region (5′ UTR) followed by the presence of ORFs (ORF 1a/1b) containing genes for synthesis of nsp required in replication;

Table 2. Comparisons on Genomic Structure of Three Coronaviruses

Genome characteristics	*SARS-CoV*	*MERS-CoV*	*SARS-CoV-2*
Length of nucleotides	29,727	30,119	29,903
Structural proteins	4 (spike, envelope, membrane, and nucleocapsid)	4 (spike, envelope, membrane, and nucleocapsid)	4 (spike, envelope, membrane, and nucleocapsid)
Number of nonstructural proteins	5	16	15
Number of Accessory proteins	8 (ORF 3a, 3b, 6, 7a, 7b, 8a, 8b, 9b).	5 (ORF3, 4a, 4b, 5 and 8).	6 (ORF 3, 6, 7a, 7b, 8, 9b).

References as cited within the text.
MERS-CoV, Middle-East respiratory syndrome-coronavirus; ORF, open reading frame.

structural genes (S, E, M, and N formation genes), certain accessory genes represented as ORF 3, 6, 7a, 7b, 8, 9b, and a 3′UTR at the end (Chen et al., 2020; Lu et al., 2020) (Table 2).

Upon comparing the two closely related viruses (SARS-CoV vs. SARS-CoV-2), the accessory protein 8a was found to be missing in the SARS-CoV-2 strain. Further variations in the number of amino acids were reported in the accessory proteins 3c and 8b (Wu et al., 2020a). It is hypothesized that a modified version of S protein of SARS-CoV has increased its binding affinity with the angiotensin-converting enzyme 2 (ACE2) receptors, the same receptors used by SARS-CoV (Gralinski and Menachery, 2020; Xu et al., 2020a). This modification may be through homologous recombination or by single N501T mutation in the S protein of the virus (Wan et al., 2020). Studies have shown SARS-CoV-2 spike's glycoprotein is a mixture of glycoproteins found on the spikes of SARS-CoV and beta-CoV (Wrapp et al., 2020; Yan et al., 2020).

Hosts and Reservoirs of CoVs

It is important to understand the origin and transmission of the virus to devise strategies for their control. SARS-CoV initially was tested positive in palm civets present in food markets of China during their outbreak in 2003 indicating them as reservoirs of this virus (Kan et al., 2005). However, the presence of anti-SARS-CoV antibodies in *Rhinolophus* bats suggested them as primary hosts in the transmission of infection (Shi and Hu, 2008).

A few years later, SARS-like-CoV was identified during ecological surveillance in the Chinese Horseshoe bats in the same region from where SARS-CoV initially spread (Banerjee et al., 2019). Serological levels of antibodies against SARS-like-CoV were found in certain patients of Hong Kong in 2001 suggesting that exposure of SARS-like-CoV to humans occurred more early than SARS-CoV but went unnoticed (Zheng et al., 2004). The human transmission was, therefore, found to have happened from bats, whereas palm civets were found as identical hosts (Kuehn, 2013).

The second outbreak of a similar kind of CoV, MERS-CoV occurred a decade later in 2012 at South Arabia where Dromedary camels were found to be the zoonotic source of this virus (Paden et al., 2018). Almost 55% of confirmed positive cases were through coming in direct contact with camels or camel-associated products (Conzade et al., 2018). According to a study, 16 out of 30 camel workers in South Arabia caught this viral infection without having any history of respiratory diseases (Alshukairi et al., 2018). Scientists were successful in isolating and culturing the live MERS-CoV from camels in Qatar (Raj et al., 2014).

However, the similarity of spike glycoprotein of MERS-CoV to that of beta-CoV and SARS-CoV suggested bats as the ancestral reservoirs of CoVs (Chan et al., 2020). Later, the virus was identified in Pipistrellus and Perimyotis bats (Annan et al., 2013). Also, some researchers had detected this virus in snakes, but close similarities of this viral strain with SARS-CoV confirmed bats as the key reservoirs (Huynh et al., 2012; Lau et al., 2013).

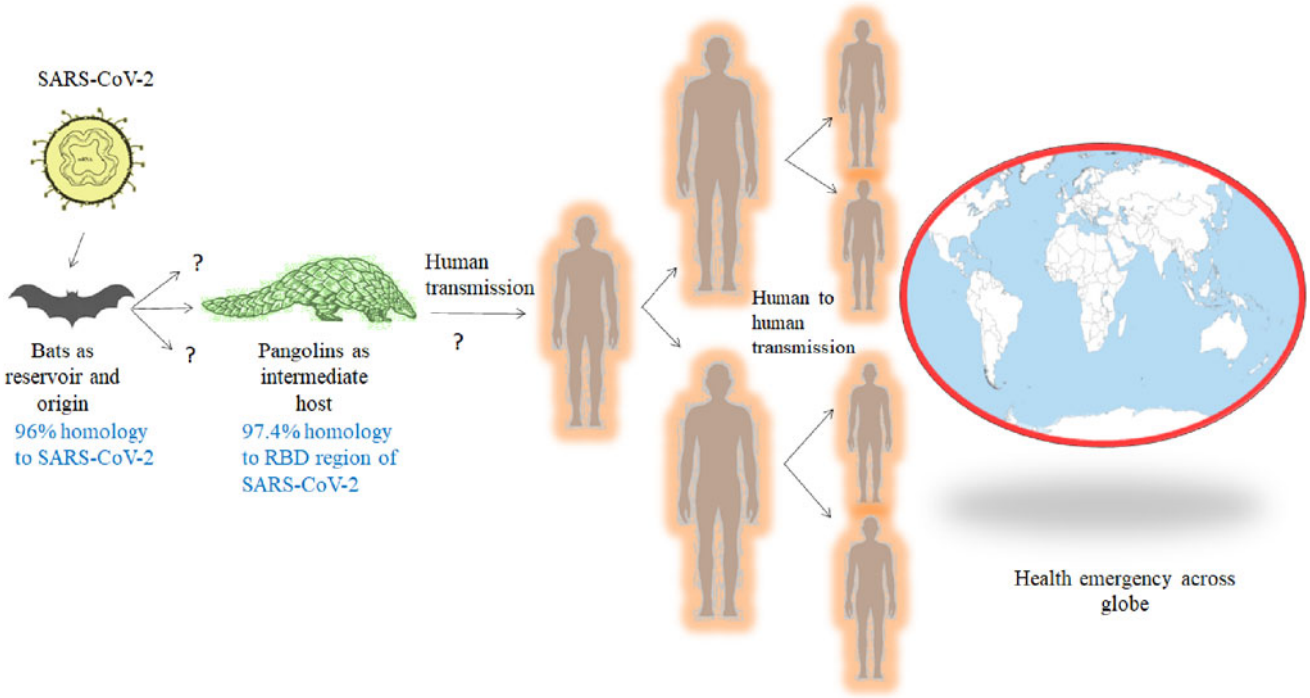

FIG. 4. Possible route of transmission of SARS-CoV-2. The sequence similarity between SARS-CoV-2 and bat CoV is about 96%, suggesting them as reservoirs. However, 97.4% of sequence similarity to the RBD region of pangolins indicates the possibility of human transmission occurred through coming in contact with the pangolins, but the way it has been transmitted is not clear yet (indicated with a question mark). Also, there could be multiple hosts from the intermediate hosts and the reservoirs and to date, not much information is available on the existence of other intermediate hosts of this virus (indicated with a question mark). Once the virus entered into the human lineage, it has spread to different countries of the world causing health emergencies across the globe. RBD, receptor-binding domain.

The recent and third outbreak of SARS-CoV-2 at Wuhan, China, has happened in 2019 and is likely to have originated from bats, but the source of transmission to humans is yet to be confirmed if it is from bats or some other intermediate hosts (Jin et al., 2020; Zhou et al., 2020). Researchers have found 96% genomic similarity of this virus with the sequences of the bat followed by that of pangolins showing 85.5% to 92.4% genome similarity (Zhou et al., 2020). However, the receptor-binding domain (RBD) in the spike protein of SARS-CoV-2 shares more similarity to pangolins (97.4%) than bats (89.2%).

Also, RBD analysis shows five amino acid similarity exists between pangolins and SARS-CoV, but only one amino acid similarity is present between bats and RBD of the virus, highlighting pangolins as intermediate hosts through which human transmission might have occurred instead of bats (Lam et al., 2020; Zheng, 2020). Minks were also reported as intermediate hosts of this virus by some researchers; however, there could be the possibility of the existence of multiple hosts through intermediate hosts, which needs to be identified further (Li et al., 2020b). The loose attachment of RBD on the spike of CoVs accounts for their ability to infect multiple hosts (Perlman and Netland, 2009; Raj et al., 2013). In Figure 4, we illustrated the possible transmission of SARS-CoV-2 from bat to human by Pangolins.

Mechanisms of Pathogenesis

A general mechanism of virus entry and its life cycle inside the host cell is shown in Figure 5 (Kumar et al., 2020). The life cycle of SARS-CoV-2 begins by binding of S protein to the ACE2—a cellular receptor on the host cells (Zhang et al., 2020a). This binding facilitates a conformational change in S protein that induces the fusion of viral envelope with the cell membrane using the endosomal pathway (Perlman and Netland, 2009). This enables the release of viral ssRNA into the host cells (Li, 2016). The viral replicase genes (ORF1a and ORF1b) of the RNA genome undergoes translation and leads to the production of two polyproteins (pp1a and pp1b) (Plant and Dinman, 2008; Ratia et al., 2006). These polyproteins are further cleaved by viral proteases for nsp production (Ratia et al., 2006). The nsp plays an important role in causing discontinuous transcription of other RNA genes of viral genome forming various mRNAs fragments (van den Born et al., 2005).

Translation of these fragments occurs in the subsequent steps and various other viral proteins are formed (Kumar et al., 2020). Finally, the assembly of viral proteins and genomic RNA occurs in the virion inside cellular organelles such as endoplasmic reticulum (ER) and Golgi apparatus (de Haan and Rottier, 2005). Then, transport of these mature virus particles occurs through vesicles, and finally, they are targeted out of the plasma membrane of the host cell and the cycle repeats after their entry into the new host occurs (Kumar et al., 2020).

In general, various viral enzymes facilitate the entry mechanisms of CoVs, including cathepsins, human airway trypsin (HAT), and transmembrane protease serine 2 (TMPRSS2), into the host cell (Bertram et al., 2011; Glowacka et al., 2011). These are cellular proteases that split the spike protein for bringing necessary changes in establishing an infection. The viral attachment is facilitated by the presence of glycoproteins on the surface of the spike. Carbohydrates or aminopeptidases are generally used as receptors by other CoVs for their entry into the host cells; however, SARS-CoV and MERS-CoV use exopeptidases (Wang et al., 2013).

In SARS-CoV-2 different membrane proteins, polyproteins, and nucleoproteins are present such as papain-like proteases, helicases, glycoproteins, RNA polymerase, 3-chymotrypsin-like protease, and accessory proteins (Wu et al., 2020b; Zhou et al., 2020). A three-dimensional structure is present in the RBD region of spike protein that maintains the van der Waals forces (Xu et al., 2020a). The specificity in the attachment of a virus occurs by recognition of 394th glutamine amino acid in the RBD of the pathogen to that of 31 lysine residue on ACE2 receptors in humans (Yuan et al., 2020). ACE2 and dipeptidyl peptidase 4 (DPP4) serve as receptors for SARS-CoV/SARS-

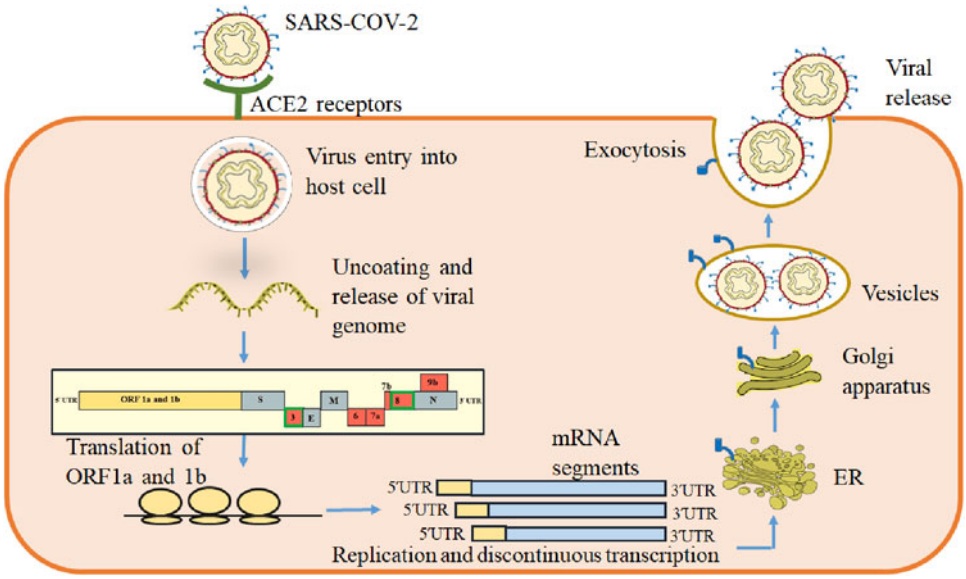

FIG. 5. Life cycle of SARS-CoV-2.

CoV-2 and MERS-CoV, respectively (Raj et al., 2013; Wang et al., 2013).

Fatality Rate

To estimate the extent to which the pandemic is going to affect the population across the globe, it becomes important to calculate the mortality rates associated with it. It indicates the proportion of people who died in a particular population, per unit time. However, in the case of epidemiology, the fatality rate is more appropriate to consider. It gives information on how many people are most likely to die or have died among all individuals who have been diagnosed positive for the disease instead of the whole population (mortality rate) for a certain period. It is also a measure of disease severity and can estimate the extent to which the disease prognosis will occur (Onder et al., 2020).

The SARS-CoV infection after originating in China in 2003 spread to 26 countries infecting 8098 individuals. It showed a fatality rate of $\sim$9% by bringing the deceased toll to 776, whereas WHO reported 14–15% of the fatality rate by this virus (World Health Organization, 2003). Years later, a more potent and highly evolved form of CoV virus, MERS-CoV began to spread in different parts of the world infecting >2428 individuals and causing 838 deaths. The fatality rate as indicated by WHO for MERS-CoV was 35% in 2012 (Adney et al., 2014).

The recent epidemiology, COVID-19, is associated with another form of CoV (SARS-CoV), which is a seventh member of this group. Since its first clinical reports in humans, it has now spread to 213 countries and territories. The viral progression is still prominent across the globe and more incubation period of this virus (14 days) makes it challenging to calculate the exact fatality rate at this moment; however, various laboratories and centers have come up for its estimation (Ruan, 2020).

Initially, 1.4% of the fatality rate was estimated by Chinese researchers on 1100 positive patients (Guan et al., 2020). Later, the Center for Disease Control and Prevention (CDC) in China had identified a fatality ratio of 2.3% after analyzing data sets of 44,672 confirmed cases in the country (The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020). Once the number of confirmed laboratory cases reached to 55,924, a Joint Mission on COVID-19 run by WHO and China had estimated the fatality rate of 3.8% (World Health Organization, 2020).

CDC has also identified certain essential points that determines the rate of a fatality such as age (0.2% for people in the age between 11 and 19 years and 14.8% for people >80 years old), gender (2.8% in males and 1.7% in females), country (depends upon control, prevention strategies, mitigation policies, preparedness, and status of health care systems), comorbid state (5.6% for cancer, 6.0% for hypertension, 6.3% for a respiratory disorder, 7.3% for diabetes, and 10.5% for cardiovascular diseases), and severity of transmission (2.9% in Hubei province, whereas 0.2% in other areas of China) (The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020).

Delay in detection and diagnosis by many countries has been a prime reason for their increased fatality rates (Verity et al., 2020). According to the recent trends, people >60 years of age and the ones having health complications are most likely to show a higher death rate (The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020; World Health Organization, 2020).

As per a report published in The Lancet Infectious Diseases by Robert Verity, it is important to consider the time duration between onsets of symptoms to death and between onsets of symptoms to hospital discharge in case of recovered patients. Therefore, 1.4% of the fatality rate was calculated after taking 17.8 days as the mean duration of onset of symptoms to death and 24.7 days as a mean of onset of symptoms to discharge of the patients. This study was conducted on 3556 cases in the mainland of China and 1334 cases outside of the mainland (Verity et al., 2020).

Multiomics Strategies

Different strategies could be employed to study infectious diseases with a major focus on multiomics biology at present (Hasin et al., 2017). This is a broad and rapidly evolving area that covers the genomic, transcriptomic, proteomic, and metabolomic studies from the past, and now various integrations and diversions within the field suggest their potential in better apprehension of organisms for attaining the global health security toward the mankind and its associated interactions. Proteomics and multiomics research are rapidly leading in the postgenomics medicine world (Pinu et al., 2019). Various omics techniques that have the potential to elucidate COVID-19-associated features and mechanisms need to be studied in detail for better addressing and controlling the pandemic (Ray and Srivastava, 2020).

Fang et al. suggest the future of multiomics research resides in the application of RNA sequencing and proteomics for characterization of the understudied organisms whose genomes are not decoded yet (Fang et al., 2016). Also, transcriptomic analysis of the SARS-CoV-2 genome has the potential to highlight the key areas that could represent one of our prime vaccine candidates in the future (Sawicki et al., 2007).

Davidson et al. (2020) performed RNA sequencing through transcriptomic analysis, and proteomic and phosphoproteome studies through tandem mass spectroscopy. They have found that the cleaved subunits of S-protein mediated by the furin site are required for the pathogenesis and zoonosis of SARS-CoV-2. The viral entry and exit are also strongly correlated to the presence of these functional subunits of S-protein. Their major studies revealed that SARS-CoV-2 proteins have a high potential to mutate rapidly (Davidson et al., 2020). Therefore, before proceeding for further research on SARS-COV-2, it is important to have a closer look at the genome sequence owing to their higher rate of mutations.

The integration of genomics and proteomics can now be successfully used to study the changes in the genetic and protein profile of a pathogen that can help in the identification of universal candidates for therapeutic purposes (Advani et al., 2019; Heunis et al., 2017). Whole-genome sequencing and proteomic techniques together constitute the development of microbial proteogenomics for a deeper understanding of pathogenic microorganisms of clinical interest (Advani et al., 2019).

Apart from genetic, transcriptomic, and proteomic studies, understanding the evolutionary pathways and strategies of microorganisms showing a higher rate of evolution is a prerequisite for controlling their high mutational rates. Such studies provide a deeper overview of mutations that a genome undergoes to harbor more virulent properties (Rao et al.,

2019). Zhang et al. (2020b) has isolated SARS-CoV-2 from a different set of patients and has characterized them into clade I (patients with a history of the visit to the seafood market in Wuhan) and clade II (patients who do not have a prior visit to the seafood market). Upon comparing the patients of two clades, he found that the rate of substitution for ORF8 and N gene in SARS-CoV-2 was higher than other accessory proteins, but the genome was relatively stable (Andersen et al., 2020).

Although pathogenesis associated with COVID-19 was not much related to the variations among the genome-reduced levels of $CD3^+$ T lymphocytes were correlated to the production of IL-6 and IL-8 cytokines imparting the virulent characteristics (Xu et al., 2020b). The likely mechanism of association between viral replication, lymphocytopenia, and bursting of cytokine storm is unclear at this moment suggesting the possibility of directing the research toward the identification of roles of the viral and host factors and their associated interactions for understanding the immunological responses behind the severity of SARS-CoV-2 infection (Datta et al., 2020; Sallenave and Guillot, 2020).

After profiling of a pathogenic organism through multiomics strategies, a key challenge that awaits is to devise mechanisms in controlling the growth of zoonotic pathogen either through therapeutic strategies or by manipulations of their culturing conditions. Electroculturomics, a study of the effect of electric modulation on microbial growth and life cycle, holds a promising future in treating human diseases when combined with probiotics, pharmaceuticals, and various nutraceutical elements (Kambouris et al., 2018).

This technique employs electrical impulses in an organism to manipulate their growth rates (Poltawski and Watson, 2009). It is a relatively new omics field analogous to pharmaceuticals that intend to use different electric modulations in restoring the impaired biological functions (Kambouris et al., 2017). Despite the rare utilization of this approach, its successful results in controlling the growth rate of fungi suggest its potential be used as an effective means for controlling the viral spread as well. The only limitation is that proper settings required for manipulating the growth rates would need to be identified (Stathoulias et al., 2020).

Since primates have been closely associated with various zoonotic outbreaks in the past, the intensity of human–primate interfaces must be taken care of to prevent the risk of zoonosis in the future (Morse et al., 2012). Primatologists should work on the forefront to reduce the demand of primates as pets and to stop their illegal trading in the markets (Karesh et al., 2005). Education about the risks, unsafe practices, and biosafety protocols associated with the primates interaction must be communicated to the people for reducing the aggression between them (Gilardi et al., 2015; Muehlenbein and Wallis, 2014). More research should be directed toward reducing the exposure of zoonotic pathogens by devising the biosafety protocols and, finally, more funding is required in this field of study if we want to reduce the global risk of zoonotic infections emerging from human–primate interfaces in the future (Lappan et al., 2020).

Conclusion and Future Directions

Why a certain strain is potentially more pathogenic in comparison with the other viral strains of CoV? What genetic modifications may result in SARS-CoV-2 showing higher transmission rates than its other counterparts? To what extent the genetic mutations have occurred and are likely to occur in the future? The answers to these questions need to be addressed to control the recent pandemic as well as in preventing the future zoonosis outbreaks in the 21st century.

Currently, comparative genomics of SARS-CoV versus MERS-CoV versus SARS-CoV-2 has revealed differences in the number of nsp and accessory proteins. However, their functional roles in pathogenesis are still being studied extensively. The genomic variations might be the reason for a certain strain of CoV to possess additional and enhanced pathogenic traits; for example, the fatality rate exhibited by MERS-COV was higher than the SARS-CoV versus SARS-CoV-2, but the transmission rate of SARS-CoV-2 is more than the other CoVs probably because of differences in their genetic structures.

The functional roles of all the variations that exist between the three zoonotic CoVs must be studied in detail both on genomics and proteomics level. The expression of the varied proteins in hosts must also be analyzed to generate a deeper understanding of how these proteins are functioning and interacting with other proteins to decipher their multiomics approach in pathogenesis.

The major setback currently is that we are unaware of what causes a CoV genome to mutate and to evolve in a new strain after every decade. If we can identify the possible reason, source, and the rate of mutation a CoV genome is undergoing by comparing the genomic structures of past and present viral strains, then we might be able to prevent future evolution of CoVs.

Through this review, we provided new insights and information on comparative genomics for three zoonotic CoVs whose outbreaks have occurred in the past and in current times. The developments on the genomic level are detailed and the potential questions that should be addressed for progress toward achieving the planetary health remains an important aspect to be explored for future studies. In the context of integrative biology, multiomics research invites studies on the genomic, transcriptomic, and expression profiles of different proteins, their functions, and associated pathogenesis of COVID-19 for controlling the outbreak now and preventing its reoccurrence in the future.

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Abbreviations Used

ACE = angiotensin-converting enzyme
CDC = Center for Disease Control and Prevention
CoV = coronavirus
COVID-19 = coronavirus disease 2019
DPP4 = dipeptidyl peptidase 4
E = envelope protein
HAT = human airway trypsin
IFN = interferon
IL = interleukin
M = membrane protein
MERS-CoV = Middle-East respiratory syndrome coronavirus
N = nucleocapsid protein
nsp = nonstructural proteins
ORF = open reading frame
RBD = receptor-binding domain
rep = replicase
S = spike protein
SARS-CoV = severe acute respiratory syndrome coronavirus 2
TMPRSS2 = transmembrane protease serine 2
TNF = tumor necrosis factor
UTR = untranslated region
WHO = World Health Organization