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Review Article

SARS-CoV-2 and other Coronaviruses: A matter of variations

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ABSTRACT

Since the appearance of COVID-19 disease as an epidemic and pandemic disease, many studies are performed to uncover the genetic nature of the newly discovered coronavirus with unique clinical features. The last three human coronavirus outbreaks, SARS-CoV, MERS-CoV and SARS-CoV-2 are caused by Beta-Coronaviruses. Horizontal genetic materials transfer was proven from one coronavirus to the other coronavirus of non-human origin like infectious bronchitis virus (IBV) of avian. Horizontal genetic materials transfer was also from non-corona viruses like astroviruses and equine rhinovirus (ERV-2) or from coronavirus-unrelated viruses, like influenza virus type C. However, SARS-CoV-2 is identical to SARS-CoV and MERS-CoV. Interestingly, Wuhan city-SARS-CoV-2 is very similar to two types of bats Coronavirus in RdRp nucleotide sequence to RdRp of SARS-CoV-2 suggesting possible transmission from bats. Moreover, many genomic mutations are found in SARS-CoV-2 genomes suggesting the mutations are developed and the virus is constantly changed. The newly discovered SARS-CoV-2 has a new open reading frame (ORF) that encodes for thirty-eight amino acid peptide chains and has no similar sequence in all reported NCBI data regarding respiratory viruses. The short peptide can serve as an identification target for SARS-CoV-2 detection.

Introduction

In February 2020, a new epidemic disease was announced by the World Health Organization (WHO) called COVID-19 caused by a unique type of coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It's a public health emergency of international concern (PHEIC) (1), which is named by the Committee on Taxonomy of Viruses (ICTV) as(SARS-CoV-2). The virus causative agent of COVID-19 is RNA viruses that belonged to the Coronaviridae family, Orthocoronavirinae subfamily, Nidovirales order. The Orthocoronavirinae subfamily is subdivided into four genera: alphacoronavirus, betacoronavirus, delta coronavirus, and gammacoronavirus (2). Coronaviridae members are the pathogen of enteric, respiratory, neurological, and hepatic diseases in many animals, namely cats, cattle, bats, and camels. (SARS-CoV-2) is the ninth known coronavirus that infects humans and the seventh recognized recently (3) and caused about 7.5 % of human respiratory diseases (4). Common cold human coronaviruses are designated as HCoV-OC43(belonged beta-CoVs), HCoV-HKU1; HCoV-NL63, and HCoV-229E (belonged alpha-CoVs). serious human infections can be caused by the Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, Severe acute respiratory

syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome-related coronavirus (MERS-CoV) (all belong to beta-coronaviruses). The symptoms may have ranged from mild to severe respiratory symptoms. Other non-respiratory symptoms and mortality may reach one-third of the cases. SARS-CoV-2 is an RNA virus sensitive to solvents of lipids, heat, and ultraviolet radiations (5).

The new SARS-CoV-2 genome of Wuhan city patients with pneumonia is 89% similar to bat coronavirus (CoVZXC21) in nucleotide sequences and 82% is the percentage the similarity to previously identified SARS-CoV of humans (6), hence it is called SARS-CoV-2. Despite that the way by which the virus emerged is not entirely identified, the genomic sequence analysis suggests that it may be originated from bat coronavirus (5). Although a short last time passed since the development of this disease until now, many studies have been performed to determine the virus on the molecular level and comparison with other coronavirus discovered in other humans and other animals. The recent review highlighted the similarity and differences between different SARS-CoV-2 and other coronaviruses discovered around the world.

CORONAVIRUSES

Coronavirus is a member of the Coronaviridae, order Nidovirales (7,8). Coronaviridae family is divided into four genera of viruses: alpha-coronaviruses and beta-coronaviruses which considered as mammals pathogens, delta-coronaviruses are affected avian and mammals and gamma-coronaviruses affect avian (9,10). The first genus belongs to Coronaviridae is Alphacoronavirus which include porcine gastroenteritis coronavirus, porcine respiratory coronavirus, human coronavirus NL63 (HCoV-NL63), Porcine epidemic diarrhea virus, Human coronavirus 229E, Scotophilus bat coronavirus 512,and Miniopterus bat coronavirus HKU8 (9). While beta-coronaviruses are the SARS-CoV, SARS-CoV-2, human coronavirus OC43, Human coronavirus HKU1, mouse hepatitis coronavirus (MHV), bat coronavirus, Rousettus bat coronavirus HKU9, Hedgehog coronavirus 1 (EriCoV), Murine coronavirus and bovine coronavirus (BCoV) (9). Delta-coronaviruses and gamma-coronaviruses are porcine delta coronavirus (PdCV) and avian infectious bronchitis coronavirus (IBV). Two alpha and two beta coronaviruses are produced by mild symptom diseases. The two beta-coronaviruses are HCoV-OC43 and HCoV-HKU1 and the alpha-coronaviruses are HCoV-229E and HCoV-NL63. Whereas, three others are cause diseases with severe symptoms namely MERS-CoV, SARS-CoV, and SARS-CoV-2. The genome of coronavirus is single-strand RNA, positive-sense, and about 26400 to 31700 bases (11). The viral RNA contains a 5′ methylated cap as well as a 3′UTR-poly (A) tail. Coronavirus genome organization is at first 5′-leader-UTR-replicase/transcriptase region then spike envelope followed by the membrane (M) and nucleocapsid (N) at the last of the strand 3′UTR-poly (A) tail are present (figure 1) (12). Coronavirus encodes for 2 types of structural proteins, spike protein (S) and hemagglutinin-esterase protein (HE) both are associated with the envelope. These two proteins are protruded from the virus envelope making the virus look like a crown. The functions of these spikes are determination of the host of the virus, mediation of virus entry, tissue tropism, and immune system induction (13).

Viral subgenomic RNA synthesis occurs in the host cells in vesicles as well as polypeptides 1a(pp1a)/ polypeptides 1ab (pp1ab) synthesis in a complex replication-transcription manner. Typically, two open reading frames (ORF1a and ORF1b) out of six ORF are responsible for pp1a and pp1ab production respectively. The two polypeptides produce sixteen non-structural proteins (nsps) by the action of papain-like proteases, or chymotrypsin-like protease (3CLpro) or main protease (Mpro). The structural proteins, like nucleocapsid proteins, membrane, and spikes, are encoded by the two mentioned ORF as well as other ORFs (5). The nsps of coronavirus interfere with the response of the innate immune of the host (14). The assembly and release of Coronavirus are mediated by the envelope while the viral glycoprotein spikes (S) are essential for the connection of the virus to the receptors of the cell (15). The subunit of glycoprotein spike-2 (S2) of SARS-CoV-2 (a fusion peptide) is well conserved so it could be a good target for Coronavirus treatment. Contrary to the receptor-binding domain which is quite different among the Coronaviruses. The ORF3b and ORF8 (secreted proteins) of SARS-CoV-2 also showed no homology with The ORF3b and ORF8 of SARS-CoV-1 (16).

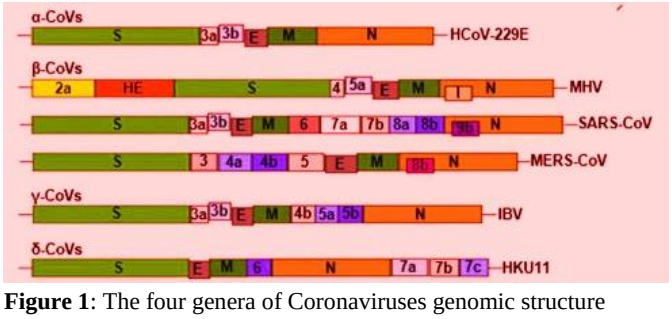

Figure 1: The four genera of Coronaviruses genomic structure

The figure shows the genomic structure of four genera of Coronaviridae (alpha, beta, gamma, and delta) with some examples of each genus, HcoV-229E example of alpha-coronaviruses, MHV, SARS-CoV, and MERS-CoV are examples of beta-Coronaviruses, IBV an example for gamma- Coronaviruses, HKU11 an example for delta-Coronaviruses. S=spikes, M=membrane, E=envelope, N= nucleocapsid (the structural proteins). HE= hemagglutinin-esterase. HcoV-229E= human coronavirus 229E, MHV= murine hepatitis virus, SARS-CoV= severe acute respiratory syndrome coronavirus, MERS=Middle East respiratory syndrome-related coronavirus, IBV= infectious bronchitis virus, HKU11= Hong Kong University virus. The figure is adapted from Fehr and Perlman (11).

Replication of Coronavirus

The virus corona is a virus with an envelope that usually replicates in the host cytoplasm (17). At the beginning of the infection, the viral spikes attach to its cognate receptors on the host cells.

The virus entry is mediated by endocytosis and this is accomplished by the cell protease cleavage of the spikes (18). Then, the viral ORFs at the 5′-end are translated into long polypeptide then the polypeptide is cleaved by proteases of viral origin to form several nonstructural proteins (nsps) like viral RNA dependant RNA polymerase (RdRp), helicase, and adenosine triphosphatase (ATPase). These enzymes are important in the replication of the virus (19). The 5′ cap of the viral genome is mediate genomic RNA attachment with the ribosome of the cell before translation (12). The lack of proofreading activity of the RdRp enzyme is compensated by another enzyme, exoribonuclease, which is one of nsps (20). The negative-sense RNA is synthesized from viral positive-sense RNA by RdRp then the negative-sense RNA is transcribed into positive-sense mRNAs while positive-sense RNA will become the viral progeny. The ribosome of the host will translate the viral mRNAs into accessory proteins and structural proteins. The E, M, and S structural proteins of the virus move into the Golgi apparatus where the M proteins direct the interaction of the protein important in viral assembly followed by nucleocapsid binding, and the virus exited from the cell via exocytosis (12).

The similarity of coronavirus with other viruses

When the observers take a glance at the sequence of the SARS genome, deposited into the GenBank (AY274119.3), they found a 41-bp conserved s2m (stem-loop II) region at The 3′ untranslated region. The s2m motif was also observed in three different viral diseases including infectious bronchitis virus (IBV) of avian, astroviruses as well as equine rhinovirus (ERV-2) (19). The conservation of the s2m motifs in the SARS, IBV, and ERV-2 viruses and the evolutionary distance between IBV and ERV-2 viruses may refer to horizontal genetic materials transfer from one to each other (21). The s2m phylogenetic distance between the s2m of IBV and the s2m of the SARS suggested that the s2m motif of SARS Coronavirus has been acquired through horizontal genetic materials transfer also (22). the s2m function is not exactly known, but some theories assume their overlap with the machinery of infected cells translation, contribution to gene regulation, and protection of virus RNA from enzyme degradation (23)

The HE protein is required for viral entrance (24). The gene of HE, occurs in subgroup A of Betacoronavirus and is located at the S gene upstream and the ORF1ab downstream regions. They believed that the Coronavirus HE gene is obtained from another virus namely influenza virus type C. Thus, the Coronavirus gene acquisition from other viral families is previously reported and this occurs by heterologous recombination (22). The HE gene's exclusive presence in subgroup A of Betacoronavirus but not in other Betacoronavirus subgroups (B, C, and D) may indicate that the recombination events may occur in subgroup A members' ancestors after subgroup A emerges from B, C and D subgroups ancestor (11).

Similarity and differences among coronaviruses

Since the SARS CoV-1 virus was discovered in 2003 many sequences of Coronavirus genomes are appeared and are deposited in the GenBank, giving advantages to the researchers to analyze and compare the conserved genomics database with their obtained data (11). The complete SARS Coronavirus genome sequence is listed on the website http://www.bcgsc.ca/bioinfo/SARS; http://www.cdc.gov/ncidod/sars/sequence.htm, and showed quite a difference between this virus and other known Coronavirus (25). The genome of the mouse hepatitis virus was the first Coronavirus genome sequenced. Later the genomes of another Coronavirus were sequenced at least ten Coronavirus genomes. Moreover, the SARS coronavirus (which appeared in China in 2003) genome is the most notable diverse genome among the studied Coronavirus genomes (26, 27, 28). Since 2003 up to fifteen new types of Coronavirus were observed and their genomes were sequenced. Out of these fifteen Coronaviruses only two were disseminated worldwide which are HCoV-HKU1 and HCoV-NL63 (29, 30, 31). The GC% of Coronaviruses ranged from 32% to 43% thus may be due to gene modification of the viral genome [32, 33). The genomes of Coronavirus compose of two-terminal untranslated regions located at the 3′ and 5′ ends, as well as organized coding regions, started from 5′-replicase ORF1ab, S, E, M and ended with N-3′ as well as many other ORFs may present according to Coronavirus subgroup in additional to a sequence of transcription regulator at 3′ ends (34).

The coronaviruses ORF1ab are translated from ORF1a and ORF1b. The translation takes place by a -1 ribosomal frameshift at the terminal site of the slippery sequence. The produced polyprotein is cleaved by the action of some proteases as described earlier to produce fifteen to sixteen nsps according to the Coronavirus group interestingly, many newly discovered cleavage sites were discovered [31,32].

The papain-like protease (PLpro) is one of nsps with an essential function. Subgroup A of Betacoronavirus and Alphacoronavirus members have two papain-like proteases (PL1pro and PL2pro) and differ from other coronaviruses that have only one papain-like protease. The conserved protein genes are served as a tool for phylogenetic investigations frequently. Moreover, some Coronaviruses (like BCoV, HCoV-HKU1and IBV) showed cleavage of their S protein (spike) into S1 and S2 (11). Different ORFs are discovered on the genomes of Coronaviridae members, small ORFs are located in the downstream region of the nucleoprotein gene like ORFs of feline infectious peritonitis virus that are implicated with viral virulence (35). Other small ORFs are found in the SARS-CoV genomes like ORF3a and ORF8 and both are variable. The human SARS-CoV ORF8 has a 29 base pairs deletion when compared with civet SARS-CoV ORF8 making a considerable diversity between the two Coronaviruses (36).

The recent study of Zhang and his colleagues (37) found that Pangolin-CoV spike-1 (S1) is related to the S1 of SARS-CoV-2 more than S1 of rat-coronavirus (RaTG13). The Pangolin-coronavirus and SARS-CoV-2 have the five same amino acids implicated in spike-host receptor interaction. The SARS-CoV-2 differs from both RaTG13 and Pangolin-CoV in that SARS-CoV-2 has a motif of furin recognition sequence at the cleavage site of the S1/S2. In general, the SARS-CoV-2 is 91.02% identical to Pangolin-CoV and the latter is 90.55% identical to RaTG13.

The overall similarity among Coronaviruses is studied as an estimated percentage of identity and by Phylogenetic analysis. There are two bat Coronavirus are related to SARS-CoV-2 bat-SL-CoVZXC21 (accession no. MG772934.1) and bat-SL-CoVZC45 (accession no. MG772933.1) they show the similarity of about 89-88% respectively. Interestingly, SARS-CoV-2 is less similar to MERS-CoV (50%) and SARS-CoV (79%) (38,39,40). Phylogenetic

analysis of Wuhan city -SARS-CoV-2 applied by Chen et al (41) indicates that Rhinolophus Coronavirus (BtCoV/4991-bats Coronavirus) is 98.7% similar to RdRp nucleotide sequence to RdRp of SARS-CoV-2 (GenBank KP876546). On the other hand, SARS-CoV-2 is 87.9% similar to bat-SL-CoVZXC21 and bat-SL-CoVZC45. Another study found that the SARS-CoV-2 is 96% similar to bat-coronavirus (42). Chen and his colleagues (41) and based on the genetic analysis of different viral genes suggested that the SARS-CoV-2 is a novel virus transmitted to man from other animals. Table 1 summarizes the similarities and differences among four Coronaviruses genera.

Table 1: Overall structural features of four Coronaviruses genera

Coronaviruses Genera	N downstream small ORF	N upstream small ORF	GC% of genome	Range of hosts	Number of NSP	Number of proteases
Alpha	0-2	1-4	34-42%	Humans, bats, pigs, cats	16	2
Beta	0 (2 in D subgroup only)	1-7	32-43%	Humans, bats, pigs, mice, horses, cows	16	1-2
Gamma	0	4-8	38-39%	Chickens, turkeys	15	1
Delta	3	1	38-43%	Bulbuls, thrushes, munias	15	1

ORF: open reading frame, N: nucleocapsid, NSP: non-structural proteins. The data in the table is the summary of the article references

Human SARS-COV2 genomes differences worldwide

GenBank and other database recorders publish several whole-genome sequences of SARS-CoV-2 aiming to uncover the source of the SARS-CoV-2 infections worldwide whether the source is of animal origin or genetically developed human coronavirus. The earliest analysis of genomic SARS-CoV-2 is done by Wu et al (43) by viral genomic phylogenetic analysis they discovered that the SARS-CoV-2 was related (89.1%) to a group of SARS-CoV that had previously been discovered in bats in China. The mutation in the spike gene may be the way by which the SARS-CoV-2 adapted to be an infectious agent to the human being. Angeletti and his colleagues (16) analyze the nsp2 and nsp3 of SARS-CoV-2 at the ORF1ab and they discovered that the glycine was substituted by serine at the 723 position of nsp2 polypeptide and isoleucine was substituted by proline at 1010 position of nsp3 due to ORF1ab mutations.

In a unique huge study, eighty SARS-CoV-2 variants were isolated from many countries worldwide (China, USA, Japan, South Korea, Taiwan, Australia, and Nepal). The C>T and T>C transition mutations are the most predominant mutations. The 8782C>T and 28144T>C variants are the most predominant and discovered in the same non-Wuhan isolates. The nsp3 mutations (within ORF1ab) were more predominant than other nsps (44). The mutations in nsps are of great concern hence the nsps may be targeted by treatment strategies (such as inhibition of protease). Before the COVID-19 outbreak and a study found that the SARS virus has developed twelve distinctive variants carrying papain-like protease (nsp3) has a role in virulence development (45). Interestingly, a unique ORF was observed in the SARS-CoV-2 genome which is called ORF10. This ORF encodes for thirty-eight amino acid peptide chains and has no similar sequence in all reported NCBI data regarding respiratory viruses. The short peptide can serve as an identification target for SARS-CoV-2 detection. The functions of this short protein are recommended to be studied (44).

Conclusion

From all reviewed information the conclusions are that horizontal genetic materials transfer is expected from one coronavirus to the other coronaviruses or even from coronavirus-unrelated viruses. Coronaviruses nsps are also differed among the family members due to mutations occurrence. Moreover, different open reading frames (ORFs) are discovered on the genomes of Coronaviridae members. Two small ORFs are discovered in both SARS-CoV-2 and SARS-CoV genomes but differ from each other and other respiratory coronaviruses. SARS-CoV-2 is related genetically with particular bat coronavirus but not to SARS-CoV and MERS Coronaviruses. Based on the genetic analysis of different viral genes suggested that SARS-CoV-2 is a novel virus transmitted to humans from other animals. Even in the same SARS-CoV-2 type, many genomic mutations are discovered in isolates collected from different countries suggesting the mutations are consensually developed. The mutation in the spike gene may be the way by which the SARS-CoV-2 adapted to be an infectious agent to a human being.

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