

Chapter 13

Emergence and Reemergence of Severe Acute Respiratory Syndrome (SARS) Coronaviruses



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Abstract The positive-strand RNA viruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and recently emerged COVID-19 epidemics, demonstrated the transmission capability of the coronaviruses by crossing the species barrier and emergence in humans. The source of coronavirus disease 2019 (COVID-19) is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), firstly reported in December 2019 at Wuhan, China. COVID-19 is a kind of viral pneumonia. The outbreak of SARS-CoV-2 (COVID-19) has been reported as the introduction of the third highly pathogenic coronavirus which crossed the species barrier and spread into the human population. Severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) were the first two epidemic viruses, respectively, in the twenty-first century. Introduction of the 2019 novel coronaviruses (2019-nCoV) in human population is a worldwide concern, and this might have generated via RNA recombination among the previous reported coronaviruses. The COVID-19 is spreading in an alarming rate, and till date no vaccine or specific medicines are available in the market. The newly emerged coronavirus COVID-19 is strongly related to SARS-CoV except little dissimilarity. In this chapter, we will discuss about the alterations and variations in antigenicity, structural changes, and RNA recombination which might be responsible for the COVID-19 emergence.

Keywords Coronavirus · COVID-19 · SARS-CoV · SARS-CoV-2 · Antigenicity · Glycosylation · Spike glycoprotein · RNA recombination

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Abbreviations

ACE2	Angiotensin-converting enzyme 2
DMV	Double membrane vesicle
HKU	Human coronavirus
IFN	Interferon
MERS	Middle East respiratory syndrome
NSP	Nonstructural protein
ORF	Open reading frame
RBD	Receptor-binding domain
RMSD	Root mean square deviation
SARS	Severe acute respiratory syndrome
ssRNA	Single-stranded ribonucleic acid

13.1 Introduction

Coronavirus belongs to the large family of viruses, i.e., *Coronaviridae* family and the order *Nidovirales* (Cui et al. 2019; Kumar et al. 2020; Phan et al. 2018). Genomic structures and phylogenetic relationship reveals that subfamily Coronavirinae contains the four genera alpha coronavirus and betacoronavirus which are restricted to mammals and responsible for respiratory illness in humans such as Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS coronavirus (SARS-CoV) (Cui et al. 2019; Kumar et al. 2020; Payne 2017; Phan et al. 2018). The other two genera gamma coronavirus and delta coronavirus infect both birds and mammals (Cui et al. 2019; Kumar et al. 2020; Payne 2017; Phan et al. 2018). SARS-CoV and MERS-CoV show severe respiratory diseases in humans, and four others (HCoV-NL63, HCoV-229E, HCoV-OC43, and HKU1) cause normal upper respiratory illness in the hosts which are immunocompetent, even though some can induce severe infections in elders, young children, and infants (Cui et al. 2019; Cascella et al. 2020). Alpha and betacoronaviruses can give rise to intense burden on animals; these include recently emerged swine acute diarrhea syndrome coronavirus (SADS-CoV) and the porcine transmissible gastroenteritis virus and porcine enteric diarrhea virus (PEDV) (Cui et al. 2019; Banerjee et al. 2019).

Continuous development and urbanization increases the frequent integration of many different animals in crowded and populated places may have made easy the emergence and reemergence of a number of these viruses (Lau and Chan 2015; <https://www.ncbi.nlm.nih.gov/books/NBK45714/>). On the other hand, high mutation and recombination rates are reported in coronaviruses, which may allow the coronaviruses to cross the barrier of species and adopt to new hosts (Lau and Chan 2015; https://clarivate.com/wp-content/uploads/dlm_uploads/2020/01/CORONAVIRUS-REPORT-1.30.2020.pdf; Liu et al. 2020).

The 2003 SARS epidemic has awakened the world's researchers and scientists on the transmission capability of the coronaviruses from animals to humans. The

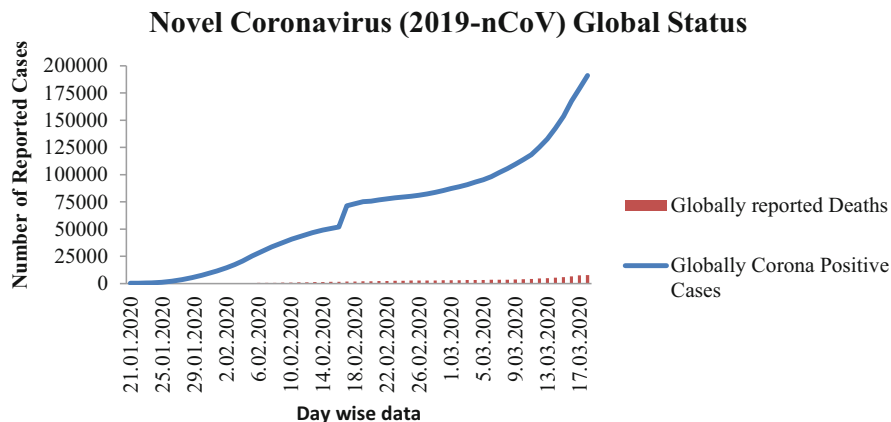


Fig. 13.1 Total reported confirmed cases and deaths due to novel coronavirus (2019-nCoV). (Data taken from <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>)

primary reservoir of the SARS-CoV is horseshoe bat (Lau and Chan 2015; Wang et al. 2006). Current sequence databases revealed the animal origin of the human coronaviruses: MERS-CoV, SARS-CoV, HCoV-229E, and HCoV-NL63 are considered to have originated in bats (Cui et al. 2019; Wang et al. 2006). SARS-associated coronaviruses are found in bats from China and worldwide continuously (Lau and Chan 2015).

Recently in 2020, SARS-CoV-2, a novel coronavirus has emerged from China which affect globally with a total of 191,127 confirmed cases and 7807 deaths (as of March 18, 2020) (Kampf et al. 2020; https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200314-sitrep-54-covid-19.pdf?sfvrsn=dcd46351_6). Figure 13.1 represents the total reported confirmed cases and deaths due to novel coronavirus (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>). The current pandemic of coronavirus-linked acute respiratory disease known as coronavirus disease 19 (COVID-19) is the third recognized spillover to humans through animal coronavirus in only the last two decades (<https://doi.org/10.1038/s41564-020-0695-z>; Kampf et al. 2020). Table 13.1 represents the discovery of human coronaviruses.

The viruses of the family Coronaviridae contain enveloped and positive-stranded RNA (Li et al. 2020; Coutard et al. 2020). Coronaviruses have the largest 26–32 kilobase (kb) positive-sense RNA genome (Li et al. 2020; Kumar et al. 2020; Shoeman and Fielding 2019). The four major structural proteins [membrane (M), envelope (E), spike (S), and nucleocapsid (N)] which create complete virus particle, encoded by the genome (Kumar et al. 2020; Wu et al. 2020; Guo et al. 2020).

The evolution and emergence of novel coronaviruses are mostly due to the lack of proofreading mechanism in RNA recombination among the present coronaviruses (Kumar et al. 2020). The S gene which encodes viral spike (S) glycoprotein has been proposed the higher frequency of recombination (Kumar et al. 2020). The novel coronavirus is closely related to bat SARS like betacoronavirus. Although, the

Table 13.1 Recent discoveries of human coronaviruses

Virus	<i>Coronavirinae</i> genus	Cellular receptor	Host	Location	Year	References
<i>HCoV-229E</i>	Alphacoronavirus	Human aminopeptidase N (CD13)	Bats	–	1966	Lim et al. (2016), Kahn (2005), Cui et al. (2019), Human Coronavirus Types (2020); https://www.cdc.gov/coronavirus/types.html ; Clarivate Analytics (2020)
<i>HCoV-OC43</i>	Betacoronavirus	9-O-Acetylated sialic acid	Cattle	–	1967	Lim et al. (2016), Kahn (2005), Cui et al. (2019), Hulswit et al. (2019), Human Coronavirus Types (2020); https://www.cdc.gov/coronavirus/types.html ; Clarivate Analytics (2020)
<i>SARS-CoV</i>	Betacoronavirus	ACE2	Palm civets, bats	China	2003	Lim et al. (2016); https://www.who.int/ith/diseases/sars/en/ ; Cui et al. (2019), Adnan Shereen et al. (2020), Parrish et al. (2008), Human Coronavirus Types (2020); https://www.cdc.gov/coronavirus/types.html ; Clarivate Analytics (2020)
<i>HCoV-NL63</i>	Alphacoronavirus	ACE2	Palm civets, bats	The Netherlands	2004	Lim et al. (2016), Cui et al. (2019); Rasool and Fielding (2010), Human Coronavirus Types (2020); https://www.cdc.gov/coronavirus/types.html ; Clarivate Analytics (2020)
<i>HKU1</i>	Betacoronavirus	9-O-Acetylated sialic acid	Mice	Hong Kong	2005	Lim et al. (2016), Cui et al. (2019), Hulswit et al. (2019), Human Coronavirus Types (2020); https://www.cdc.gov/coronavirus/types.html ; Clarivate Analytics (2020)
<i>MERS-CoV</i> (Middle East respiratory syndrome)	Betacoronavirus	DPP4	Bats, camels	Saudi Arabia	2012	Lim et al. (2016), Cui et al. (2019); Human Coronavirus Types (2020); https://www.cdc.gov/coronavirus/types.html ; National Foundation for Infectious Diseases (2020) Coronavirus. https://www.nfid.org/infectious-diseases/coronaviruses/ ; Clarivate Analytics (2020)
<i>COVID-19</i>	Betacoronavirus	ACE2		China	2019	Lim et al. (2016), Kumar et al. (2020), Adnan Shereen et al. (2020), Tai et al. (2020), Human Coronavirus Types (2020); https://www.cdc.gov/coronavirus/types.html ; Clarivate Analytics (2020)

longer spike protein of 2019-nCoV has remarkable difference when compared with the bat SARS-CoV and SARS-like coronaviruses (Kumar et al. 2020). In this chapter, we will discuss about the emergence and reemergence of the SARS coronaviruses and genetic variations from SARS-CoV to SARS-CoV-2.

13.1.1 SARS-CoV to SARS-CoV-2: RNA Recombination, Antigenic Shift, and Antigenic Drift

Reported phylogenetic analysis revealed the close relationship between COVID-19 and Bat SARS-like coronavirus (Lu et al. 2020; Kumar et al. 2020). Although both emerged from the SARS coronavirus, suggesting the newly spread 2019-nCoV into human is very much related to SARS-CoV (Kumar et al. 2020). Figure 13.2 represents the evolutionary relationship between different lineage of betacoronavirus and their respective cellular receptors through which they interact with the host cell. As per sequence alignment data, the sequence of spike glycoprotein of COVID-19 and SARS-CoV shows 76.2% individuality, 87.2% resemblance, and 2% gaps. This data indicates that COVID-19 spike glycoprotein exhibits higher sequence similarity with 12.8% of variation with SARS-CoV. The study performed by Kumar et al. (2020), on variation of sequences of minimal receptor-binding domain (RBD), revealed 73.3% uniqueness, 83.9% matches, and 0.4% gaps, suggesting a difference of 16.1% and tertiary structure of minimal receptor-binding domain. COVID-19 may have changes in virus-binding capacity shift and infectivity into the receptors of the host cell, due to notable deviation in minimal RBD of S-glycoprotein.

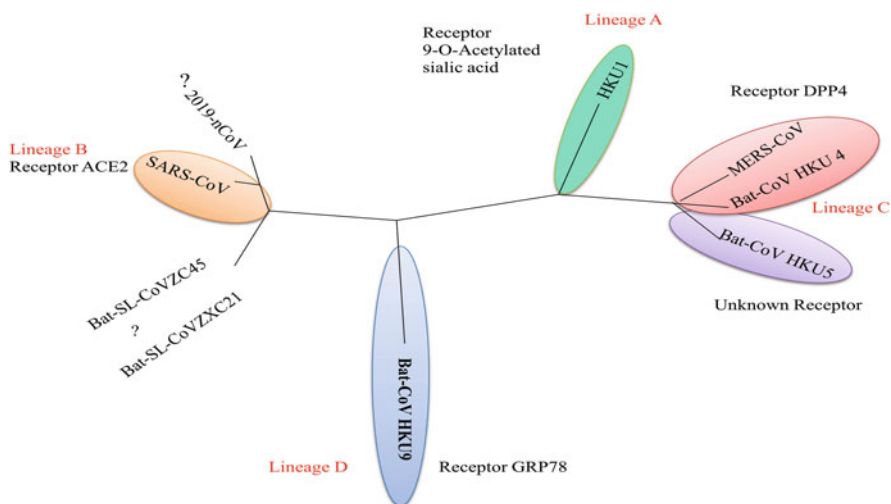


Fig. 13.2 Evolutionary relationship between different lineage of betacoronavirus and their respective receptor

13.2 Structure of Genome

The viruses belong to *Coronaviridae* family enclosed envelope and positive-stranded RNA (Li et al. 2020). Coronaviruses have the largest 26–32 kilobase (kb) positive-sense RNA genome. The genome of coronaviruses contains open reading frames (ORFs) of variable number (6–11). In the first ORF, two thirds of the total viral RNA are located. Upon infection, two large precursor polyproteins, namely pp1a and pp1ab, has been translated by viral genome in the host cells. These translated precursor polyproteins get processed into 16 mature nonstructural proteins (nsp1–nsp16) by viral proteinases. These nonstructural proteins have been numbered according to the position from N to C terminus (Kumar et al. 2020; Narayanan et al. 2014). Figure 13.3 depicts the structure of coronavirus representing essential proteins, accessory proteins, and nsp1–16. The remaining ORFs encode accessory proteins. The remaining part of viral genome encodes spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid protein (N). All these four are essential structural proteins. S protein is attached to the host receptor ACE2, including two subunits S1 and S2. The cellular tropism by RBD and virus host range is determined by S1. Virus cell membrane fusion is determined by S2 (Guo et al. 2020; Pradhan et al. 2020; Belouzard et al. 2009; Du et al. 2009).

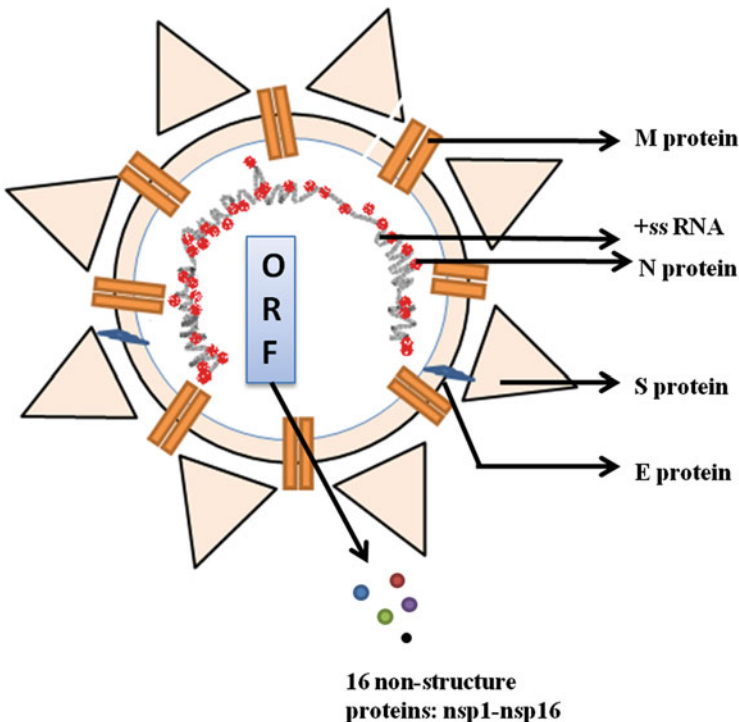


Fig. 13.3 Structure of coronavirus causing severe acute respiratory syndrome

Transmembrane nutrient transport and formation of envelop were performed by M protein. N protein and E protein along with several accessory proteins obstruct with host immune response (Guo et al. 2020; Pradhan et al. 2020). The nonstructural proteins play a vital function at the time of viral RNA replication and transcription (Kumar et al. 2020; Narayanan et al. 2014). The assigned functions of these 16 mature nonstructural proteins are mentioned in Table 13.2. Several nsps are

Table 13.2 Functions of 16 mature nonstructural proteins which play central role at the time of viral replication

Nonstructural protein	Allocated function	Reference
nsp1	IFN signaling inhibition, degradation of cellular mRNAs, translation inhibition, cell cycle arrest	Chen et al. (2020), de Groot et al. (2012), Kamitani et al. (2006), Huang et al. (2011)
nsp2	Unknown; associates with RTCs	Chen et al. (2020), de Groot et al. (2012)
nsp3	Papain-like proteinase; polyprotein processing; ADP-ribose-phosphatase (macrodomain); RNA-binding; antagonist to interferon (IFN); host innate immune response blocking	Chen et al. (2020), de Groot et al. (2012)
nsp4	Unknown; double membrane vesicle (DMV) formation	Chen et al. (2020), de Groot et al. (2012)
nsp5	Main proteinase M, polyprotein processing; inhibition of IFN signaling	Chen et al. (2020), de Groot et al. (2012)
nsp6	Unknown; DMV formation; restriction of autophagosome expansion	Chen et al. (2020), de Groot et al. (2012)
nsp7	ssRNA binding, cofactor with nsp8 and nsp12	Chen et al. (2020), de Groot et al. (2012)
nsp8	Cofactor with nsp7 and nsp12, primase	Chen et al. (2020), de Groot et al. (2012)
nsp9	ssRNA binding; associates with replication-transcription complexes (RTCs), dimerization	Chen et al. (2020), de Groot et al. (2012)
nsp10	Dodecameric zinc finger protein; associates with RTCs, stimulates nsp16 methyltransferase activity, scaffold protein for nsp14 and nsp16	Chen et al. (2020), de Groot et al. (2012)
nsp11	Unknown	Chen et al. (2020), de Groot et al. (2012)
nsp12	Primer-dependent RdRp	Chen et al. (2020), de Groot et al. (2012)
nsp13	Helicase; RNA 5'-triphosphatase	Chen et al. (2020), de Groot et al. (2012)
nsp14	3' → 5' exoribonuclease; guanine-N7-methyltransferase (RNA cap formation)	Chen et al. (2020), de Groot et al. (2012)
nsp15	Endoribonuclease; evasion of dsRNA sensors	Chen et al. (2020), de Groot et al. (2012)
nsp16	Ribose-2'-O-methyltransferase (RNA cap formation)	Chen et al. (2020), de Groot et al. (2012)

unique enzymes implicated in one or more important step(s) in viral replication. Other nsps appear to be entirely involved in virus–host interactions (De Groot et al. 2012).

Coronavirus SARS-CoV-2 is positive ssRNA and enveloped virus. Genome encodes 16 nonstructural proteins (NSPs) and 4 essential structural proteins and several accessory proteins.

13.3 Alteration in Glycosylation Pattern of Spike Glycoproteins

The comparison of the glycosylation sites between COVID-19 and SARS-CoV of the spike glycoproteins unveiled the presence of novel glycosylation sites in COVID-19, such as NGTK, NFTI, NLTT, and NTSN (Kumar et al. 2020). The presence of novel glycosylation sites in COVID-19 might be due to the variation in sequence. Along with the deviation in reported four glycosylation sites, i.e., NGTK, NFTI, NLTT, and NTSN, COVID-19 spike glycoprotein exhibits the similar glycosylation sites, also present in SARS-CoV (NITN, NGTI, NITN, NFSQ, NESL, NCTF, and NNTV). There is a possibility of interaction between COVID-19 and host receptor through novel glycosylation sites which may have an effect on the process of internalization and linked pathogenesis (Kumar et al. 2020).

13.4 Antigenic Variation in Spike Glycoproteins

A study carried out to determine the antigenicity by comparing the antigenic variations in both spike glycoproteins of COVID-19 and SARS-CoV revealed the individuality of most of the CTL epitopes in COVID-19 compared to the SARS-CoV. However, six identical epitopes RISNCVADY, CVADYSVLY, RSFIEDLLF, RVDFCGKGY, MTSCCCLK, and LKGVKLHY are present in spike glycoprotein of COVID-19 and SARS-CoV (Kumar et al. 2020). In COVID-19, some epitopes are identified with difference in single amino acid change. As per available information and research data of antigenicity, COVID-19 shows little antigenic similarities with SARS coronavirus. It is possible that antigenic similarity may cause similar antigenic response, and therefore, it can be used as one of the precautionary approach. Variation and similarity in spike glycoprotein and epitopes may be useful to design newer and effective vaccines (Kumar et al. 2020).

13.5 Structural Difference in Spike Glycoproteins

The length of encoded proteins in COVID-19 and SARS-like coronaviruses was found nearly same (Guo et al. 2020). However, longer spike protein of COVID-19 showed a notable difference compared to the bat SARS-like coronaviruses and SARS-CoV. On the whole 12.5% of difference in sequences of S glycoprotein and difference in minimal RBD with 23.6% may cause structural differences in spike glycoproteins of COVID-19 and SARS-CoV (Kumar et al. 2020). The studies performed to measure the average distance between the molecules of superimposed proteins, i.e., RMSD, depict the 1.38 Å local RMSD value between two glycoproteins. This illustrates regardless of 12.8% sequence variation that there is an insignificant structural divergence among the spike glycoproteins of SARS-CoV and COVID-19. The absence of structural divergence in spike glycoproteins of SARS-CoV and COVID-19 raises a hope for the treatment of brutal COVID-19. As there is structural similarity in SARS-CoV and COVID-19, the previously trialed and tested attachment inhibitor used for SARS-CoV can be used as the present choice of treatment for COVID-19 (Kumar et al. 2020).

13.6 RNA Recombination in Positive-Strand RNA Viruses

Genetic recombination is an important evolutionary mechanism in positive-strand RNA viruses. Recombination drives toward the diversity in viral genome by the creation of novel chimeric genomes (Bentley and Evans 2018; Lorige and Holmes 2012). Irrespective of single- or multiple-segment genome, RNA recombination may occur in the entire RNA viruses (Lorige and Holmes 2012). Cross-species transmission in RNA viruses is the most common approach to get entered into a new host. The process of recombination assists the entry of viruses as it facilitates viruses to explore a larger proportion of the sequence area, than mutation. This increases the probability of finding a genetic configuration that assists host adaptation (Lorige and Holmes 2012). Both replicative and non-replicative recombination mechanism works for the viruses. In replicative recombination, the major role is played by viral polymerase; however, other viral or cellular proteins may exist. On the contrary, cellular components are solely responsible for non-replicative recombination (Bentley and Evans 2018).

Recently emerged many human diseases are originated from RNA viruses. There are three mechanisms by which viruses go through evolutionary changes. These are mutations also known as antigenic drift, re-assortment (antigenic shift), and recombination (Shao et al. 2017). The emergence of viral diseases in human exhibits active viral genome recombination or re-assortment. Coronavirus that emerged in turkey was a recombinant infectious bronchitis virus which attained a spike protein-encoding gene from coronavirus 122 (Lorige and Holmes 2012). There is a possibility of emergence of COVID-19 through RNA recombination.

Executive Summary

- The third epidemic of the twenty-first century:
 - SARS-CoV was reported as the first epidemic of the twenty-first century in 2003 following by MERS-CoV in 2012.
 - COVID-19 caused by SARS-CoV-2 is the third epidemic which is declared pandemic by the WHO.
- Severe acute respiratory syndrome (SARS) and coronavirus disease 2019 (COVID-19) portray a number of similarities:
 - Virus homology: As per sequence alignment data, the spike glycoprotein sequence of COVID-19 and SARS-CoV shows 87.2% resemblance; sequences of minimal receptor-binding domain (RBD) show 83.9% similarity.
 - Presence of similar glycosylation sites and similar epitopes.
 - Routes of transmission of both the viruses (i.e., contact, droplets, and fomite).
- Along with the similarities, severe acute respiratory syndrome (SARS) and coronavirus disease 2019 (COVID-19) depict a number of dissimilarities also:
 - Such as 12.5% of difference in S glycoprotein sequence and difference in minimal RBD with 23.6%.
 - Other behavioral differences, such as rate of transmission and severity of COVID-19 is much higher than SARS-CoV.
- The emergence of novel coronavirus 2019 (COVID-19) might be due to RNA recombination as the positive-sense RNA viruses are well reported for their ability of RNA recombination which make them potent to cross the species barrier.
- The structural similarity of COVID-19 with SARS-CoV could be encashed in terms of:
 - Use of available treatment for the inhibition of attachment with the host cell. This could be an effective way to control the spread of disease.
 - Can use some drug/compound to block the entry into host cell by binding to the receptor.

13.7 Conclusions

The newly emerged coronavirus SARS-CoV-2 is strongly related to the predecessor SARS-CoV. SARS-CoV is becoming pandemic which is declared as public health emergency of global concern. The presence of novel glycosylation sites in SARS-CoV-2 makes it possible to become pandemic due to its antigenic divergence. At this

time, it is important to understand and educate the mass to follow the instructions given by the authorities and avoid any social gathering. By this at least we can delay the transmission in widespread community. Slowdown of transmission rate will provide time to the researchers and scientists to prepare well and develop vaccine and treatment for this novel coronavirus. The similarity of SARS-CoV-2 to SARS-CoV in terms of antigenic sites proposes the scope of SARS-linked peptide-based vaccine to prevent COVID-19. The structural similarity of SARS-CoV-2 to SARS-CoV suggests the use of attachment inhibitor, specific to coronavirus as the current option of the treatment. Although the mechanism of species to species transfer of the SARS coronavirus is difficult to understand, SARS-CoV 2003 epidemic makes it clear that animal coronaviruses are budding threats to the human community. Still researches are going on COVID-19. Limited information on novel coronavirus makes some boundaries to explain the complete antigenicity and structure of COVID-19.

13.8 Future Perspectives

Complete genome analysis is required to understand the similarities and differences of SARS-CoV-2 with the previously reported viruses. Complete genome analysis also helps in the development of vaccines and medicines against COVID-19. It is required to understand and do the complete research on the emergence and reemergence of coronaviruses and to understand the change in proteins and genome. Transmission through crossing the species barrier is another area to focus on.

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