

Review Article

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Genome Organization and Pathogenesis of SARS-CoV-2

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ABSTRACT

The causative agent of COVID-19 disease is a novel betacoronavirus called as SARS-CoV-2 (severe acute respiratory syndrome), which emerged as a pandemic of global concern. World Health Organization i.e., WHO on 11th of March, 2020 declared a worldwide emergency as the number of cases increased at high rate. Still no effective antiviral therapy is available for the treatment of this disease hence; it is the clarion call of time to develop a vaccine to combat this disease. The causative agent of this disease is enveloped single strand positive sense virus that belongs to family Coronaviridae. The phylogenetic analysis revealed that this virus originated from bats, and belongs to Coronavirinae family. The genome of coronavirus is approximately 30kb and has 6-11 ORFs which encode 9680 amino acid polyproteins, among which first ORF codes for 16 nonstructural proteins (nsps) whereas other ORFs code for accessory and structural proteins. SARS-CoV-2 enters into the host cells by binding of the spike glycoprotein with the ACE2 receptor, similar with that of SARS-CoV. The pathological mechanism used by SARS-CoV-2 is similar to that of SARS-CoV and MERS-CoV viruses. So, to develop antiviral therapeutics as well as preventive measures, it is important to understand the genome organization, complexity and replication mechanism of this virus. Therefore, this review mainly focuses on the genome structure as well as the mode of pathogenesis of this virus.

Keywords

SARS-CoV-2, Pandemic, COVID-19, ORFs, MERS-CoV, Nonstructural proteins

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Introduction

Genome Organization of SARS-CoV-2

SARS-CoV-2 (Severe acute respiratory syndrome), is a positive sense single-stranded RNA virus belonging to family Coronaviridae and order nidovirales. The genome of coronavirus is ranging from range of 26 to 32 kb and consists of 6–11 open reading frames (ORFs) which encodes as many as 9680

amino acid polyproteins (Guo *et al.*, 2020). The First ORF (open reading frame) of SARS-CoV-2 genome accommodates approximately 67% of its genome which encodes 16 nsps (nonstructural proteins) and 9 accessory proteins (Gordon *et al.*, 2020; Wu *et al.*, 2020). The SARS-CoV-2 viral genome completely lacks the hemagglutinin esterase gene but comprises of two flanking UTR (untranslated region) at the positions 265 (at 50 end) and 358 nucleotides (at 30 end)

respectively. Multiple sequence alignment of SARS-CoV-2 and SARS-CoV clearly revealed absence of significant difference in their open reading frames as well as non structural proteins. The major nsps includes papain like protease (nsp3), protease (nsp5), chymotrypsins-like proteases as well as Well as nsp12 (RNA dependent RNA polymerase) and nsp13 (helicase) involved in replications/transcription process (Chan *et al.*, 2020). The structural proteins of SARS-CoV-2 includes S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins that are required to make complete virion particle.

Morphogenesis, assembly and budding of SARS-CoV-2 are dependent on the activity of M and E protein respectively whereas spike S glycoprotein is mainly involved in the fusion process. S glycoprotein consists of two subunits S1 and S2 where S1 subunits showed 70% sequence identity with that of bat SARS CoV as well as with the humans SARS-CoV, that is also composed of signal peptide, N-terminal domain (NTD), and receptor-binding domain (RBD) of viral genome (Walls *et al.*, 2020). The S2 subunits of Spike glycoprotein shares almost 99% sequence identity with that

of bat and human SARS-CoV which is made up of HR-N and HR-C (2 hepted repeat region) that is required for the coiled-coil structures covered by protein ectodomain (Figure 1).

Entry and SARS-CoV-2 replication in host cells

Introduction of SARS-CoV-2 into host cells depends on interaction or binding of spike protein with the receptor present on the cell surface as well as priming activity of S protein by protease of host cell. Wrapp *et al.*, 2020 has reported spike protein of SARS-CoV-2 showed 20 times greater affinity in comparison with of SARS-CoV-2. Spike protein binding to the ACE2 receptor creates conformational alterations in spike protein structure, leading to the fusion of envelop protein of virus with the host cell membrane following entry through endosomal pathway (Coutard *et al.*, 2020; Matsuyama and Taguchi 2009). Consequently, viral RNA release into the cytoplasm of host which further undergoes translation resulting in the generation of polyproteins such as pp1a and pp1b cleaved by viral proteases into small protein molecules.

Fig.1 Pictorial representation of Genomic organization of SARS-CoV-2. Coronavirus genome ranges from 26 to 32 kb and consists of 6–11 open reading frames (ORFs). Additionally, four major structural proteins including spike surface glycoprotein (S), membrane, nucleocapsid protein (N), envelope (E) and accessory proteins like ORFs

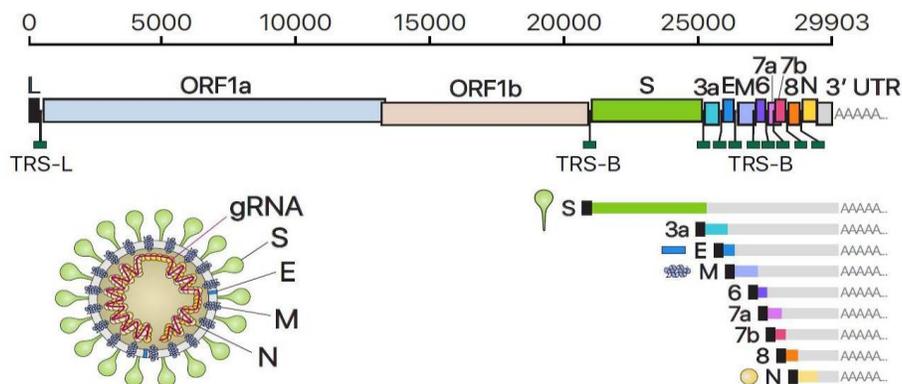
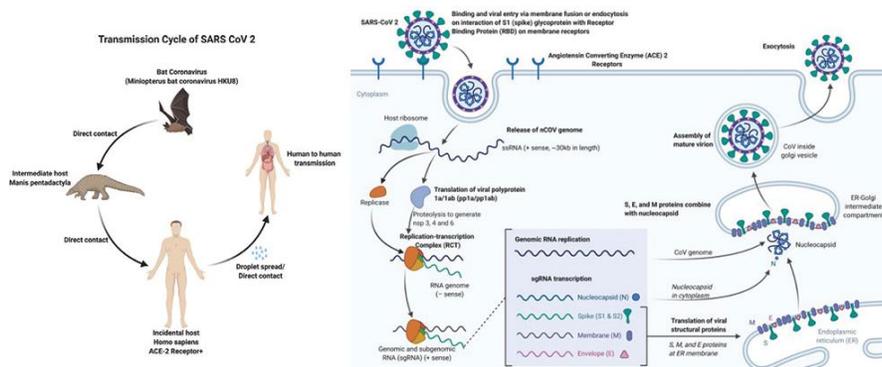


Fig.2 SARS-CoV-2 entry and replication in host cells. SARS-CoV-2 enters the target cells by binding of spike glycoprotein to ACE2 receptor



Coronavirus replication involves, shifting of ribosomal frame during the process of translation and produces both genomic and several copies of subgenomic RNA molecules by discontinuous transcription. Assembly of virion particle occurs via interaction of viral RNA and protein at cell organelle like endoplasmic reticulum (ER) and Golgi complex. These newly formed virions are then released out of the cells with the help of vesicles (Hoffmann *et al.*, 2020).

Pathogenesis

Pathological findings suggests that SARS-CoV and MERS-CoV infected patients showed high level of resemblance with each other. The human coronaviruses is transmitted via the respiratory tract, mostly by aerosols and also by sneeze droplets. The virus is mainly localized in the upper respiratory tract as the optimum temperature for viral growth is 33-35°C. Flow cytometric analysis of blood samples exhibits significant decline in the count of CD4 and CD8 T cell. X-rays images showed rapid progression of pneumonia in chest region with little differences observed between right and left lung. Patients having symptomatic COVID-19 infection show a rise in neutralizing as well as complement fixation titers of antibody in the serum after

inoculation that waned after months. The lower part of respiratory tract is seldom involved, however, pneumonia may occur. Asthmatic children may be suffering from wheezing attacks, and adults with severe pulmonary disease. HCoV-OC43 can also infect neurons results in cause encephalitis (Figure 2).

In conclusion the SARS-CoV-2 belongs to the family Coronaviridae, having 30 kb genome size approximately the genome of SARS-CoV-2 comprises of 14 ORF sequences, encoding 29 proteins. Viral genome encodes 16 non structural proteins (nsp) and 9 accessory proteins including viral replication/transcription mediating protein; the RNA dependent RNA polymerase (RdRp) (also called as nsp12). SARS-CoV-2 uses the ACE2 similar as SARS-CoV receptor for internalization. Histopathological analysis of tissues from SARS-CoV-2 infected patients exhibits virus-induced cytopathic effect with symptoms of acute respiratory distress syndrome.

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