British Journal of Research
ISSN: 2394-3718

Open Access Research Article

Pathogenesis of SARS-CoV-2 and its Variants

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ABSTRACT

COVID-19 is a major health concern globally. The virus found to have zoonotic transmission with latency period of the virus is 2-14 days. These viruses majorly infect the type 2 pneumocystis in the alveoli of lungs by binding to the Angiotensin Converting Enzyme 2 (ACE-2) with the help of spike proteins. The virus divides and replicates using host organism's replication machinery and get released into the surrounding cells by exocytosis. In response to the virus, the host body release inflammatory mediators which results in cytokine storm and leads to high fever and impaired oxygenation.

Keywords: Cytokine storm; Hemagglutinin esterase; Small membrane; Angiotensin converting enzyme; Nucleocapsid

INTRODUCTION

Coronaviruses called after the crown like shape on the outer surface and infects both animals and human. It has been divided into three genera or groups based on its serological cross reactivity and the same was confirmed through genomic analysis which was later used for nomenclature by the international committee on taxonomy of viruses in 2009. Coronaviruses contains the largest known positive strand RNA genomes of sizes ranges 30-32 kb. The replicas locus encoded within 5 end and the structural protein at the 3' end of the genome following an order of Hemagglutinin Esterase (HE) (HE is only present in some beta coronaviruses) followed by spike (S), small membrane (E), Membrane (M) and Nucleocapsid (N) and Internal (I) protein, encoded within the N gene. While assembly spike proteins arranged themselves in trimmers forming polymers embedded in envelope forms a structure of crown. Replicas gene contains two large motifs namely ORF1a, ORF1b encompassing two third of the genome and on translation encodes for two large polyproteins pp1a and pp1b respectively [1-5].

MATERIALS AND METHODS

SARS-CoV-2

In December 2019, Wuhan city in China reported several cases of pneumonia in hospital with the patient having the symptoms of dry cough, fever. On January 7, Chinese researchers identified a new viral disease as the origin of acute infection. At the end of January 2019, the genomic sequences analysis was perform between different classes of coronaviruses. It shared 79.6% similarity to SARS-CoV and 50% with MERS-CoV sequences, followed by 96% genome sequence similarity between Bat-CoV-RaTG13 and SARS-Cov-02 which proved to be a potential suspect for transmission of the disease, however, in January 22, 2020 after WHO delegate visit, it was strongly support as human

Received:	14-May-2022	**Manuscript No:**	IPBJR-22-13452
Editor assigned:	16-May-2022	**PreQC No:**	IPBJR-22-13452 (PQ)
Reviewed:	30-May-2022	**QC No:**	IPBJR-22-13452
Revised:	20-October-2022	**Manuscript No:**	IPBJR-22-13452 (R)
Published:	27-October-2022	**DOI:**	10.21767/2394-3718.9.12.123

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Citation Bohra M, Rani U, Murugan N (2022) Pathogenesis of SARS-CoV-2 and its Variants. Br J Res. 9:123.

transmission. Due to increase in number of cases worldwide in March 2020, WHO declares it as a global public health emergency? [6-8].

Structure

Like other coronavirus species, SARS-CoV-2 composed of four main structural proteins namely "S" protein (Spike glycoprotein), "N" protein (Nucleocapsid protein), "E" protein (Envelope glycoprotein), and "M" protein (Membrane glycoprotein) along with sixteen non-structural proteins (nsp1-16). The primary function of spike protein of any virus is to attach itself to the receptors available on the surface of cell membranes of host organisms which varies from species to species. SARS virus has a receptor binding domain that targets a particular receptor called ACE-2 with a greater affinity rate. Carbohydrates molecules present in spike protein facilitate the conformational changes on binding with the receptor which allows the virus to get inside by endocytosis. Spike proteins consist of two functional subunit S1 and S2. S1 unit contains N-Terminal Domain (NTD) and Receptor Binding Domain (RBD). S2 unit comprised of Fusion Peptides (FP), Heptad Repeat1 (HR1), Central Helix (CH), Connector Domain (CD), Heptad Repeat2 (HR2), Trans Membrane domain (TM), and Cytoplasmic Tail (CT). The function of S1 to bind with receptor whereas S2 is to fuse the membrane between host cells and viral to promote entry of viral nucleic acid into the host cells. The site between both subunits is always referred as S1/S2 cleavage site which is responsible for the activation of proteins which helps in fusion of both host and viral membranes through irreversible conformational changes. M protein is present abundantly on the viral surface and with other structural protein collectively decides the virus size and the structure of the virus. Membrane protein and envelope protein work mutually to form new viral particles. The capsid protein envelope that encases the virus Genome resides under the viral envelope. The primary function of N protein is not well understood, but may be involved in the transcription of the viral genome to make several new copies of the virus (**Figure 1**) [9-13].

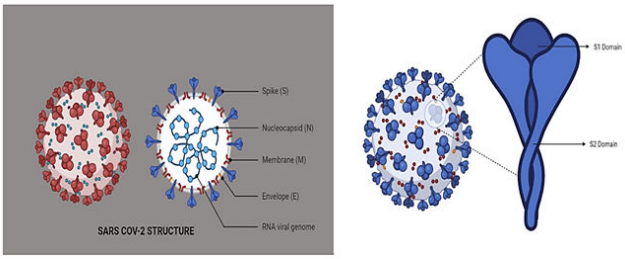

Figure 1: SARS CoV-2 structures.

Pathogenesis

The coronavirus targets and attacks the respiratory system, which is transferred from one person to another by droplets and fomites. The person who carries the virus either may be symptomatic or asymptomatic. The virus has a 2–14 days latency phase; during that time, the virus replicates itself in the lungs. The human lungs contain sacs of alveoli which is made up of two different cells; type 1 pneumocystis and type 2 pneumocystis, type 1 primary function in alveoli is in the exchange of gases, whereas type 2 pneumocystis help to produce surfactant which mainly keeps alveoli open for exchange of gases by decreasing the surface tension and reduce the collapsing pressure. The trimmers of spike proteins bind to ACE-2 (Angiotensin Converting Enzyme 2) which is highly expressed on adult nasal epithelial cells and pulmonary epithelial cells of humans. Along with S1/S2 cleavage site, host cell surface proteins such as TMPRSS2 (Transmembrane serine protease 2), furin (facilitates pH dependent entry) and endosome cathepsind B and L also helps in fusion of viral membrane into the host cell membrane. The +SSRN genome encapsulated by nucleocapsid protein inside host cell utilizes the host ribosomes to translate ORF region, ORF1a and ORF1b into replicas polyprotein pp1a and pp1b respectively. Pp1a and pp1b then undergoes proteolysis to form RTC (Replication and Transcription Complex) and to generation number of non-structural proteins which helps in amplification of viral genome and also in viral assembly. RTC comprised of DMVs (Double Membrane Vesicles), convoluted membranes and small open double membranes which creates protection environment for the transcription of sub genomic (+) RNA. RTC synthesizes both (-) RNA (serves as a template for +genomic RNA) and +RNA (sub-genomic RNA). +mRNA on translation encodes for all the structural proteins and whole viral assembly (both genomic DNA and structural proteins) occurs with the help of ER-Golgi intermediate complex which released by exocytosis to infect other cells or organisms (**Figure 2**).

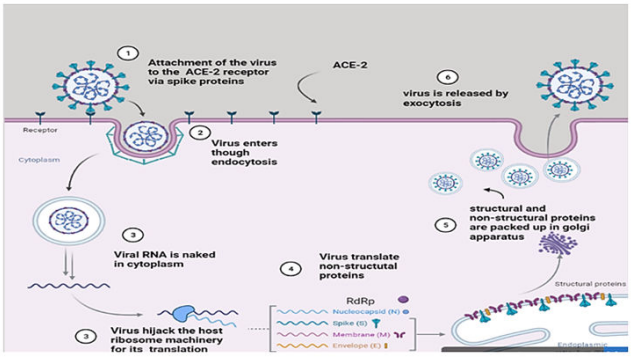

Figure 2: Illustration of pathogenesis of SARS CoV-2.

Due to the rapid replication of the virus inside the alveoli releases inflammatory mediators, which in result alert the macrophage, and once macrophages get stimulated, it secretes specific cytokines to induce protection against the virus in surrounding non infected cells. Macrophages release cytokines such as TNF-α, interleukin-1. Apart from this, cytokines such as interleukin-6, interleukin-8 and interleukin-1 are pro inflammatory cytokines and increase vascular permeability and increase adhesion molecules by dilating the endothelial cells beneath the alveolus. This leads to vasodilation increase in capillary permeability resulting the fluid inside leaked out into interstitial spaces and goes into alveoli, which shrinks or compresses the alveoli. The fluid when enters into the alveoli, drowns out all the surfactant from the alveoli, leading to high surface tension and alveoli

collapse. Due to which the patient will suffer from impaired oxygenation known as hypoxemia. Inflammatory mediators also attract neutrophils at the injury site and try to eliminate the virus by releasing reactive oxygen species known as proteases, which damages the surrounding type 1, and types 2 alveolar cells. As a result, both the gas exchange process, as well as surfactant is decreased. IL-1 and IL-6 that are produced in large amounts signals the hypothalamus to release prostaglandins. Prostaglandins, IL-1, IL-6, and TNF-α, are altogether responsible for causing fever, symptoms of infection due to COVID [14].

Variants of SARS-CoV-2

Mutation leads to variants and types of variants are recognizing based on the site where mutation have occurred. Every human body and race is different from each other, which is govern by the climate and food we food we eat and accordingly affects our immune system. The immunological responses of every individual varies and therefore pathogens need to manipulate their system to be able to survive in human body which may leads to the number of variants of SARS-CoV-2 pathogens. Spike protein mainly consists of S1 and S2 subunits. S1 Subunits contains SP (Signal Peptide), NTM (N- Terminal Domain), RBD (Receptor Binding Domain), RBM (Receptor Binding Motif) whereas S2 Subunits HR1 and HR2, TM (Transmembrane Anchor) and IC (Intracellular Tail). As per the articles published recently, most of the mutations have been observe in NTM and RBD of S1 subunits spike proteins of SARS-CoV-2 pathogens, which have been explained in details below [15].

B.1.1.7 variant

Also known as Alpha variant and was first observed in UK on November 2020. The variant consist of total 23 mutations out of which 8 mutations are seen in spike protein. As per the recent studies demonstrates, three mutations plays major role for the variation namely N501Y, spike deletion 69-70 and P681H. N501Y mutation changes the amino acid from Asparagine to tyrosine at position 501 in spike protein RBD (Receptor Binding Domain) on the other hand, spike deletion of 69-70 in the RNA genome leading to deletion of 2 amino acid in spike proteins with unknown significance. Infect P681H mutation changes proline to histidine at position 681 in the spike protein which is still unclear (**Figure 3**).

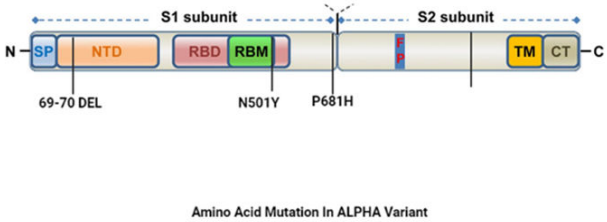

Figure 3: Amino acid mutation in alpha variant.

B.1.351 variant

It was first noticed on December 2020 in South Africa and have labeled as a BETA variant by WHO. This variant possesses numerous mutations with significant biological role. The mutation is majorly observed in receptor binding region of spike protein like N501Y in Alpha variant it forms an extra interaction with the RBD and also increased the binding affinity of the spike protein to ACE-2 receptor which in result increases infectivity. E484K mutation changes glutamic acid (E) by lysine (k) at position 484. This mutation also known as escape mutation as it improves virus ability to evade host immune system easily. K4179-E484K and N501Y mutation are examples of substitution a mutation which provides an extra but essential interaction and signifies higher infectivity in RBD (**Figure 4**).

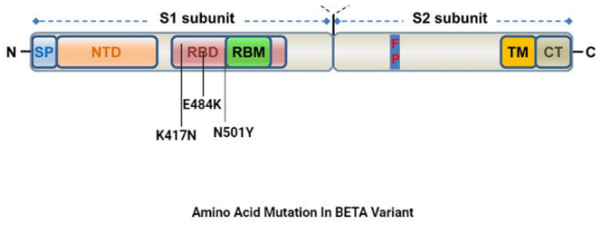

Figure 4: Amino acid mutation in beta variant.

P.1 variant

It is also known as gamma variant and was first observed in January 2021 in Brazil. The variant comprises 17 amino acid mutation and majorly concerned mutations are K417T, E484k and N501Y. The variant has 8 mutations in which 4 mutations are synonymous genetic mutation in ORF1a and ORF1b region with one deletion mutation. Gamma has ten mutations in spike protein including N501Y and E484K and also has two mutations in its ORF8 region and one in N gene. Convalescent and vaccine sera show significant loss of neutralizing activity against P.1 lineage (**Figure 5**).

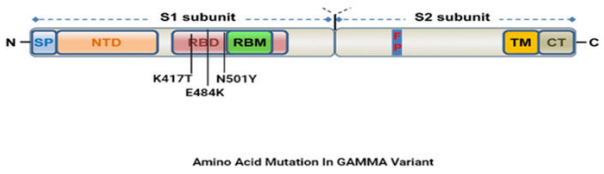

Figure 5: Amino acid mutation in gamma variant.

B.1.617.2 variant

Also known as delta variant and was first observed in India on October 2020 namely L452R and E484Q. L452R substitute Leucine (L) to arginine (R) at position 452 in spike protein which modifies the virus affinity for the ACE-2 receptor and decrease recognition capability of immune system. Another mutation, E484Q generally substitute glutamic acid (E) to glutamine (Q) at position 484 in spike protein resulting in stronger binding potential to the human ACE-2 receptor as

well as better ability to evade host immune system as compare to other variant (Figure 6).

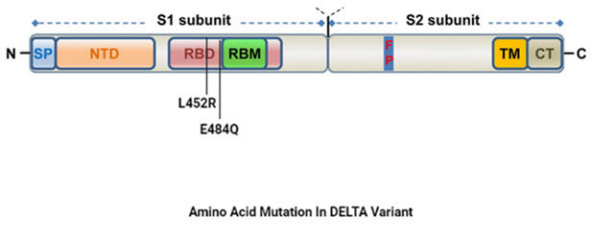

Figure 6: Amino acid mutation in delta variant.

RESULTS AND DISCUSSION

B.1.427 variant

Also known as epsilon variant and was first discovered on July 2020 in California USA. The variant has 5 defining mutation (14205V and D1183Y in the ORF1ab gene and S131, W152C, L452R in the spike protein). Epsilon is considered to be more transmissible than previous circulating variants. It shows about 20% increase in viral transmissibility (Table 1).

Table 1: Increase in viral transmissibility.

Variant	Place first identified	Date of identification	Variant name given by WHO	mutations	Transmissibility
B.1.1.7	United kingdom	Sep 2020	Alpha	N501Y 69-70DEL P681H	More than 43% compared to previous strain
B.1.351 B.1.351.2 B.1.351.3	South Africa	May 2020	Beta	N501Y K417N E484K	More than 50% transmissible compared to previous strain
P.1 P.1.1 P.1.2	Brazil	Nov 2020	Gamma	N501Y E484K K4179	25-61% transmissible compare to previous strain
B.1.617.2 AY.1 AY.2	India	Oct 2020	Delta	E484Q L452R	60% transmissible compare to previous strain
B.1.427/B.1.429	USA	Jul 2020	Epsilon	S13I W152C L452R	20% increase in transmissibility compared to previous one
B.1.525	United Kingdom/ Nigera	Dec 2020	Eta	E484K, D614G, 69del, 70del	Unknown significance
B.1.526	USA	Nov 2020	Lota	L452R, E484K, D614G	Unknown significance
B1.617.1	India	Dec 2020	Kappa	L452R, E484Q, D614G	Unknown significance
P.2	Brazil	Apr 2020	Zeta	E484Q, D614G	Unknown significance

CONCLUSION

The SARS-CoV-2 virus binds to the ACE-2 receptor with high affinity as compared to the other species of coronaviruses. Virus spike protein helps the virus to get attached to ACE2 and get into the host cell by direct fusion or endocytosis. The virus primarily targets type 2 pneumocystis in alveolar cells and replicate the viral genome within the host cell. The virus is released from the host cell by exocytosis and which infects other surrounding cells leads to the development of a cytokine storm in the body and cause impaired oxygenation in the host. The immunological responses of each and every individual are different and pathogens get adapted to the host using mutations in the genome of pathogens for survival as well as to escape the counter attacks of host immunity.

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