Vol.66: e23220261, 2023
https://doi.org/10.1590/1678-4324-2023220261
ISSN 1678-4324 Online Edition

Review - Human and Animal Health

SARS-CoV-2 Variants Impact on Key Signaling Pathways Metamorphoses into Severity

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Editor-in-Chief: Paulo Vitor Farago
Associate Editor: Marcelo Ricardo Vicari

Received: 03-May-2022; Accepted: 31-Oct-2022

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HIGHLIGHTS

- Omicron and Delta have been found to be most dominant among all variants of SARS-CoV-2.
- SARS-CoV-2 variants cause various comorbidities.
- JAK/STAT3, MAPK1, mTOR and PI3K pathways deregulated due to infection caused by different variants of SARS-CoV-2.

Abstract: The Severe Acute Respiratory Syndrome Coronavirus-2 causes a dreadful Coronavirus Disease namely COVID-19. Respiratory system is the primary target of the virus. It also impairs other major organs such as kidney, heart, liver, brain etc. Multiple novel variants of SARS-CoV-2 have appeared since the SARS-CoV-2 pandemic occurred which are linked to increased virulence, disease transmission and severity. The virus attacks the host signalling pathways to maintain a favourable environment for its spread. The present study focuses on the comprehensive analysis of major signaling pathways affected due to several variants of SARS-CoV-2 leading to abnormalities in cell growth and differentiation. The information was curated from the weblinks of several platforms like WHO, CDC, PANGO, Nextstrain clade and GISAID clade. The data on signaling pathways and comorbidities was generated by screening of different research and review articles. SARS-CoV-2 consolidates the cytoskeleton of the host for effective cell invasion and modulates the transcription processes to enable the translation of viral protein(s). These events lead to significant increase and prolonged hyper inflammation. Further, a decreased interferon (IFN) response along with increased interleukin production leading to cytokine storm is observed. Deregulation of interleukin pathways, TNF-α signalling through JAK/STAT-3 signalling, MAPK1, mTOR, PI3K are few other signalling pathways that are affected on SARS-CoV-2 infection. This review represents a comprehensive analysis of the vigorous life cycle of SARS CoV-2, its different variants affecting host signalling pathways which eventually cause dysfunctioning of several organs and development of comorbidities.

Keywords: SARS-CoV-2 & Variants; COVID-19; Comorbidities; Signaling pathways; Hyperinflammation.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2), a novel human beta-coronavirus was first detected in Wuhan, China in December 2019 that lead to the global spread of Corona Virus Disease-2019 (COVID-19) pandemic [1]. The current breakout has created extraordinary challenges for everyone and has shattered public health in various nations [2]. According to WHO, 587,396,589 documented cases of COVID-19 and 6,428,661 deaths have been reported globally as of 15 August 2022 (https://covid19.who.int/). Variability is a remarkable aspect of the outbreak which ranges from minor to life-threatening complications [3]. Modifications to the virus are being evaluated by WHO and its international networks of expertise to determine the major amino acid alterations for advising nations and the people about the precautionary measures against the spread of infection.

SARS-CoV-2 is susceptible to biological evolution as it integrates with new human host system. The establishment of new variants may have distinct features from its original strains as a result of mutations occurring throughout time. Frequent genome sequencing of viral specimen aids in the detection of novel SARS-CoV-2 genetic variations propagating in populations, particularly in the event of a worldwide pandemic. The prospect of catastrophic illness is escalated by gender, age and comorbidities [4].

The intensity of COVID-19 disease development is linked to a number of recurrent ailments [5]. The most prevalent comorbidities in COVID-19 are diabetes mellitus, hypertension, Chronic Renal/ Kidney Diseases (CKDs), Cardiovascular Diseases (CVDs), hypertension and cancer [6]. COVID-19 survivors are experiencing a growing number of long-lasting consequences. The common signaling interactions have been unfolded between COVID-19 and the comorbid conditions utilizing multi-omics data sources and bioinformatics approaches. Approximately, 100 human kinases involved in cellular physiology, metabolism and immunological activation are upregulated or downregulated by SARS-CoV-2 proteins [7].

COVID-19 infection leads to the release of cytokines and inflammatory reactions that induces common signaling pathways between diabetes, cancer, CKDs and CVDs are TLR (Toll-Like Receptors) signaling, Interleukin (IL-6 & IL-17) signaling, TNF-α (Tumor Necrosis Factor-α) signaling via NF-kB and JAK/STAT-3 signaling. These pathways in turn stimulates other pathways like MAPK1 (Mitogen Activate Protein Kinase), EGFR (Epidermal Growth Factor Receptor), mTOR (Mammalian Target of Rapamycin)/ PI3K (Phosphatadylinositol-3- kinase), Fc epsilon receptor RI (FCERI) providing gene expressions and defense against extracellular pathogens by the activation of innate immunity, cell growth, differentiation, programmed cell death, phagocytosis etc. Therefore, the present study aims towards a comprehensive analysis of affected signaling pathways due to infection caused by various variants of SARS-CoV-2 which eventually leads to signaling pathways dysfunction causing several comorbidities.

METHODOLOGY

A vigorous literature study was conducted to curate the data related to SARS-CoV-2, its variants and mutations found in its genome using Google Scholar and PubMed. In the series of literature survey 30 research articles and 31 review articles were thoroughly studied and data was compiled. World health organization (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/), CDC (https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html), PANGO (https://cov-lineages.org/), GISAID clade (https://www.gisaid.org/hcov19-variants/), Nextstrain Clade (https://nextstrain.org/ncov/gisaid/global) and ICMR (https://www.icmr.gov.in/) platforms were used to access and characterize the lineages and mutations of SARS-CoV-2. The major affected pathways due to SARS-CoV-2 infection were studied and taken into consideration. The pathways were thoroughly acknowledged and the information provided in the article is compiled from the evident and experimental research articles that focuses mainly on the variants, molecular mechanism, cross-talks of comorbidities.

Structure and life cycle SARS-CoV-2

SARS-CoV-2 is comprised of 5-8 adjunct proteins, 16 nonstructural proteins and 4 major structural proteins of the matrix: nucleocapsid (N), spike (S), membrane (N) and envelope (E) glycoprotein [8]. The surface spike (S) glycoprotein is present on the outermost layer of virion and is broken into two subunits, S_1 and S_2. S_1 is N-terminal subunit that assists the coronavirus to penetrate inside the host body and S_2 is a C-terminal subunit of Spike protein that allows the virus to integrate with the cell membrane [9]. The receptor-binding domain (RBD) and the N-terminal domain (NTD) of the S_1 subunit are involved in viral invasion into the host cell [10]. SARS-CoV-2 enters into the host cell by adhering its S_1 subunit of Spike protein (S) to the receptors of Angiotensin Converting enzyme-2 (ACE2) that are present on epithelial cells of the respiratory system like alveolar epithelial cells (Type II). ACE-2 receptors are also exhibited by some other organs like

myocardial cells, enterocytes of ileum, upper esophagus, renal tubular cells and urothelial cells of the urinary bladder [11]. Role of ACE-2 gene expression and its correlation with COVID-19 was also explored using insilico approaches [12]. Binding of virus is accompanied by preparing the S_2 subunit of spike protein with host trans-membrane serine protease-2 (TMPRSS2) to allow viral entry into the cell leading to endocytic replication of the virus to generate virions [13]. A recent insilico study aimed at understanding the relation of prostate cancer and COVID-19 have highlighted the role of variations observed mainly in ACE-2 and TMPRSS2 genes [14].

The activation of spike protein via TMPRSS2 and host proteases is the primary stage of viral life cycle [15]. This promotes the attachment of viral envelope and cell membrane to introduce virus inside the host cell [16]. The attachment of ACE-2 receptors and virions of SARS-CoV-2 undergo pinocytosis and the enzyme, cathepsin L present in the host system degrades the viral S gene by releasing the viral DNA to the cell upon ingestion [17]. Host ribosomes are used to translate the positive-sense ssRNA genome inside the cell. ORF1ab encodes pp1a and pp1ab polyproteins which release the proteases PLpro and 3CL-pro. PLpro protease has papain-like structure while 3CL-pro looks like 3C [18]. The nonstructural proteins (NSPs) 1–3 are produced by PLpro, while NSPs 4–16 are released by 3CL-pro [18]. NSP12, helicase NSP 13 and RNA-dependent RNA polymerase (RdRp) create an RNA replication complex with SARS-CoV-2 NSPs [20]. NSPs 10, 13, 14, and 16 help to cap mRNA and inspect the fledgling genome [19]. Several NSPs like NSP3, NSP1, NSPs 12, NSP13, NSP14, ORF3, ORF7a/b, and ORF6 counteract innate immunity specifically the interferon (IFN-1) pathway during the duplication of genome [20].

Signalling molecules associated with SARS-CoV-2 Infection

Toll-like receptors (TLRs) activated by the virus in the course of infection further stimulates the generation of multiple proinflammatory cytokines such as interleukins (IL-1β, IL-6, IL-2, IL-7), IFN-γ, granulocyte colony stimulating factor (GCSF) and tumor necrosis factor (TNF-α) [21]. CD4 and CD8 T cell populations were low in the peripheral blood of highly sick patients but the percentage of overexpressed T cells was high [21]. The increased number of T helper (Th-17) cells and CD-8 T cells encoding perforin and granulysin lead to hyperinflammation [22]. Th17 responses in the host are significant determinants of cytokine storms, which are a defining feature of severe COVID-19 infections [23].

The structural proteins and genetic material of the virus are organized into the virion, which utilizes blisters to reach the cellular surface of host and is discharged by Arl8b-dependent or lysosomal exocytosis. The endoplasmic reticulum chaperone GRP78/BiP of host is pushed and liberated with the entire virus particle during this event [24].

On the contrary, premature virions employ N protein to discover a glycosylated E protein on the membrane of the cell [25]. This association permits the virion to reposition itself before branching from the host organism [25]. Eventually, the breakdown of host cell organelles might result in the production of lysosomal contents, viral progeny and activation of apoptosis [26].

Global distribution of SARS-Cov-2 variants

Viral mutations are constantly evaluated by sequence-based detection technology such as experimental research and epidemiological studies. During the initial stages of the pandemic, genetic diversification of SARS-CoV-2 was limited, with the establishment of a worldwide prominent variant named D614G that was linked to enhanced infectivity and decreased disease incidence as compared to its primordial strain [27]. An additional variant was discovered in Humans, which was connected to spread from infected domesticated mink in Denmark with decreased infectivity [28]. Since then, numerous SARS-CoV-2 variants have been identified, some of which are classified as variants of concern (VOCs) and others as Variants of Interest.

WHO and Centers for Disease Control & Prevention (CDC) recognized five SARS-CoV-2 VOCs and 8 VOIs since the onset of the pandemic, owing to the introduction of numerous variants based on the most recent epidemiological report as of December 2021.

SARS-CoV-2 Variants of Concerns (VOCs)

VOCs have been attributed to greater disease transmission, virulence, or the potential to dodge diagnosis, as well as reduction in the efficiency of treatments and vaccinations. Alpha, Beta, Gamma, Delta, and Omicron are the five VOCs that contain mutations in RBD and NTD. All variants except delta variant, have the N501Y substitution on the RBD, which leads to higher sensitivity of S gene for ACE-2 receptors, boosting adhesion and subsequent penetration of virus into the host cells [29]. According to the recent publications, a single alteration of N501Y improves the binding of RBD and ACE-2 by 10-fold over the

original strain (N501-RBD). Beta and Gamma variants bearing N417/K848/Y501-RBD and ACE-2 mutations have substantially low binding ability as compared to N501Y-RBD and ACE-2 [30].

1. Alpha - The Alpha variant or GRY having B.1.1.7 lineage was previously referred to as GR/501Y.V1. This was first identified in United Kingdom after the sequencing of SARS-CoV-2 positive samples of patients in late December 2020 [31]. This variant was also detected in PCR samples from a commonly used commercial experiment that assessed for the lack of S gene resulting in S-gene target failure (SGTF). The genetic material of virus has 17 mutations. The spike (S) protein has eight mutations (69-70 & 144 deletion, P681H, N501Y, A570D, S982A, T716I, D1118H). The spike protein of N501Y has a higher specificity for ACE-2 receptors which facilitates viral attachment and ultimate penetration inside the host cells [32].

2. Beta - A novel variant of lineage B.1.351 is called Beta Variant or GH501Y.V2. The variant has nine alterations in the spike protein (L18F, K417N, E484K, N501Y, R246I D215G, D614G, D80A, and A701V). K417N, N501Y and E484K mutations are present in receptor binding domain and can elevate the adhesion capacity towards ACE-2 receptors [33]. GH501Y.V2 was identified in U.S. in January 2021. This variant is said to have a high rate of transmission rate and a low eradication rate.

3. Gamma - The P.1 variant is also called GR/501Y.V3 variant. It was first identified in United States in the start of January 2021. The S gene of the variant is mutated ten times (L18F, T20N, R190S, H655Y, P26S, D138Y, T1027IV1176, E484K, K417T and N501Y). The RBD has three mutations L18F, K417N, and E484K [33]. According to the WHO epidemiological bulletin provided by WHO on March 2021, this variety was migrated to 45 nations.

4. Delta- The variant of lineage B.1.617.2 is known as Delta. It was first discovered in India during December 2020. It contributed to the devastating second surge of SARS-CoV-2 outbreak in India in April 2021.The variant was first recognized in March 2021 in the United States and is mostly the prevalent variant in country. According to the WHO, the Delta strain was believed to be a VOI.

WHO classified the variant as a VOC in May 2021 because of its high rate of viral transmission. The spike protein of the B.1.617.2 strain exhibits ten mutations T19R, G142D*, 157del, R158G, L452R, 156del, T478K, P681R, D614G, and D950N.

5. Omicron – The variant of lineage B.1.1.529 called Omicron was reported by WHO in South Africa on November, 2021. It is followed by a significant increase in the number of cases [34]. Omicron has beyond 30 spike mutations [35]. The detected alterations involved are as follows –

- T91 present in envelope gene;
- P13L, E31del, R203K, G204R, R32del, S33del in nucleocapsid;
- D3G, A63T, Q19E in Matrix;
- G142D, N211del/L212I, Y144del, V70del, Y143 del, A67del, H69del, Y145del, and T951 in the NTD of spike;
- N501Y, Q498R, Y505H, N440K, S477N, E484A, K417N, T478K, G446S, Q493R, G496S, S375F, S371L, G339D, S373P in the RBD of spike;
- D796Y in the peptide fusion of spike protein;
- N969K, Q954H, L981F present in the heptad repeat (HR-1) of S protein and several additional alterations in the spike and non-structural proteins [35].

According to preliminary estimations, Omicron has a 13-fold higher viral load and is 2.8 times highly contagious than the Delta strain [36]. The K417 and E484A mutation is projected to hold a substantially devastating effect rendering the omicron variant to be more susceptible towards experiencing therapeutic innovations [36]. The Omicron is further divided into 5 major lineages namely, BA.1, BA.2, BA.3, BA.4 and BA.5. BA.1.1 is the sub-lineage of BA.1 which possess R345K mutation in S gene. BA.2.12.1 and BA.2.75 are sub-variants of BA.2. The sequences are derived from a common ancestral variant, hence these are homophyletic sequences. There is a difference of 50 amino acids between BA.1 and BA.2. BA.2 has a high rate of transmission all over the world than BA.1[37].

The diversification of the sub-variants of Omicron occurred in Gluteng, South Africa and were reported in February 2022. There are 39 mutations in BA.1, 40 in BA.1.1, 31 in BA.2 and 34 in BA.3 having some

similar mutations. N786K, Y505H, N211I, T95I V213R and N856K are the similar and detrimental mutations that are present in Omicron and its sub variants. BA.2.12.1 has similar spike mutations as that of BA.2 with two additional mutations S704F and L452Q. BA.2.75 also has similar BA.2 spike mutations along 9 additional mutations K147E, W152R, D339H, N460K, G446S, I210V, F157L, G257S and Q493R (reverse mutation). These mutations are characterized by the electrostatic interaction between the RBD domain and the ACE-2 receptors of the host body that increases their affinity towards human ACE-2 receptors leading to high rate of transmission [38].

BA.4 and BA.5 have evolved from BA.2 having similar mutations in S protein with 4 additional mutations L452R, Q493E, F486V and Del69-70. The binding affinity of BA.4 and BA.5 to the ACE-2 receptors is more consistent and higher than other subvariants [39]. BA.4, BA.5, BA.2.12.1 and BA.2.75 are the lineages that are under monitoring for further investigation in order to check their effect on global health of the public as compared to other viruses [40].

SARS-CoV-2 Variants of Interest (VOIs)

Variants having particular biomarkers are correlated with modifications that cause increased risk of transmission or virulence, less neutralisation by antibodies produced by antigenic infection, the potential to circumvent surveillance or a decline in medicinal or vaccine efficiency. WHO has identified eight VOIs from the start of pandemic: Epsilon, Zeta, Eta, Theta, Iota, Kappa, Lambda and Mu (Figure 1).

1. Epsilon variants- The variants of B.1.427 and B.1.429 lineage are also known Epsilon or CAL.20C/L452R. Those were first discovered in United States in June 2020 and appeared in the United States, escalating from 0% to more than 50% of decoded cases, indicating an 18.6-24% increase in disease transmission compared to untreated circulating isolates. These strains exhibit significant mutations –

• L452 R and D614G in B.1.427

• S13I, L452R, WIS2G and D614G in B.1.429.

Although it is a VOI, CDC has designated this strain as VOC based to its elevated infectiousness in United States [41].

2. Zeta- Zeta variant of P.2 lineage was discovered in April 2020 in Brazil and exhibits critical spike mutations (L18F, T20N, F157L, P26S, E484K, S929I, D614G and V1176F). CDC and WHO designated the Zeta variant as VOI based on its decreased infectivity after therapy and immunization.

3-4. Eta and **Iota-** The variants of B.1.525 and B.1.526 lineage were observed in New York for the first time in November 2020. These were assorted as VOIs owing to its counterbalance towards the rate of infection by immunization and antisera therapy. These variants exhibit critical mutations in Spike gene. Alterations in B.1.525 are E484K, Q677H, Δ144, A67V, D614G, Δ70/69, F888L and B.1.526 are S477N*, A701V*, L5F*, E484K, D614G, T95I, and D253G. Eta and Iota were recorded in November 2020 in New York. These were designated as VOI by CDC and WHO owing to the ability to minimize stabilization using antisera and vaccination techniques.

5. Theta- The variant of P.3 lineage is also named GR/1092K.V1. It is designated as a Variant of Interest by WHO because it has critical mutations- 141del/143del/142del with E484K, P618H and N501Y present in S gene. It was initially discovered in Japan and Philippines in February 2021.

6. Kappa- The variant has B. 1.517.1 lineage and significant mutations- L452R, E154K, T95I, G142D, L452R, Q1071H, P681R, E484K and Q1071H. It was recognized in India in December 2021 and is characterized as VOI.

7. Lambda- The variant of C.37 lineage was primarily reported in Peru. It has been classified as a variant of interest by the WHO in June 2021 because of high transmission rate in the region South America.

8. Mu- The variant having B.1.621 lineage was first recognized in Columbia. It was dubbed as a Variant of Interest by WHO in August 2021.

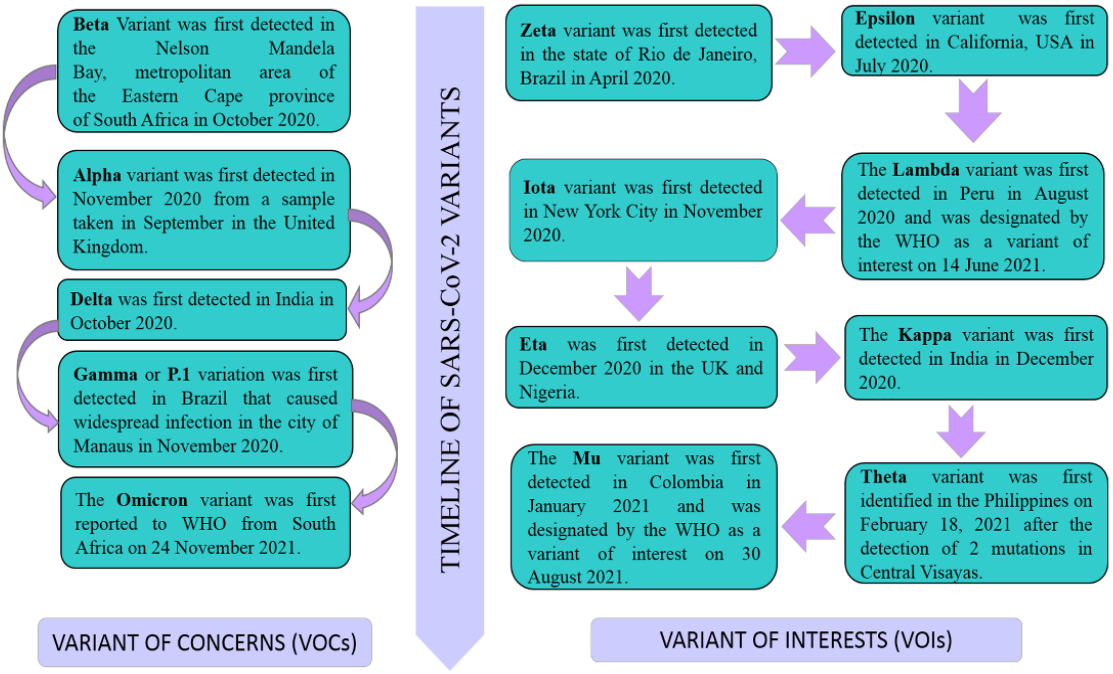

Figure 1. SARS-CoV-2 variants timeline

Effects of SARS-CoV-2 in various organs

SARS-CoV-2 mostly affects the lungs and other essential organ systems including the brain, gastrointestinal tract (GI), hepatobiliary, cardiovascular and renal systems. Direct viral toxicity, ischemia damage produced by Deep Vein thrombophlebitis (DVT), Renin Angiotensin Aldosterone System (RAAS), angiitis and immunological dysfunction are the suggested pathways that explain SARS-CoV-2-induced organ impairment [42]. The comorbidities due to SARS-CoV-2 infection are summarized below in Table 1:

Table 1. Adverse effects caused by SARS CoV-2 Infection

S. No.	Organs	Adverse effects due to SARS CoV-2 Infection
1.	Liver	• Hepatic steatosis • Hepatocyte necrosis • Nodular proliferation • Chronic congestion
2.	Kidney	• Symptoms of Renal Tubular Injury • Accidental Cell death and vacuole degeneration
3.	Heart	• Myocarditis • Vascular inflammation • Cardiac arrhythmias
4.	Lungs	• Diffused alveolar damage • Type II pneumocyte hyperplasia • Hyaline membranes • Airway inflammation • Large vascular thrombi & platelet (CD61 positive) • Fibrin microthrombi (84% cases)
5.	Gastrointestinal (GI) Tract	• Numerous infiltrated plasma cells and lymphocytes with interstitial edema
6.	Brain	• Acute hypoxia

Cellular pathway interaction with SARS-CoV-2

The SARS-CoV-2 infection leads to the activation of signaling pathways. The major cellular Signaling pathways affected due to the comorbid and SARS-CoV-2 infection are mainly, JAK/STAT, MAPK1, NF-κB and PI3K/MTOR (Figure 2). They in turn activates cell signaling pathways linked and increases the production of signalling molecules like ILs, TLR and TNFs that lead to inflammatory responses and cytokines release. These activate innate immune system by stimulating cell growth, cell division, cell survival, cellular proliferation, cyclin synthesis, angiogenesis etc. Various cytokines like IL-1β, IL-6, IFN-γ and TNF-α have been found to be exaggerated after the viral infection of SARS-CoV-2 [43]. The elevated levels of the mediators lead to Cytokine Storm resulting in tissue damage [44]. It causes overexpression of immune system and uncontrolled release of cytokines promoting inflammation against the antigens [45]. Cytokine release is initially marked by the activated state of innate immune system after the infection caused by virus. Endothelial and epithelial cells produce cytokines to obstruct viral replication whereas impaired cells are swamped by effector cells. It is also linked with generation of main cytokines and cell signaling mechanisms. IL-6 is the chief cytokine responsible for cytokine release that was reported to be escalated in the patients suffering from the viral infection after COVID-19 [46].

Out of all the reported variants till date, delta and omicron variants harbors the maximum number of mutations. The spike protein has mutation in its receptor binding domain that facilitates the binding of virus to the human ACE-2 receptor cells. The binding and viral invasion further leads to the replication of activated virus particles. The viral infection leads to the release of cytokines, chemokines, growth factors, TLRs etc. that in turn activates the inflammatory reactions in human body giving rise to tissue or cellular damage [46]. The delta has increased infectivity rate and omicron has a high transmission rate [36]. More the infection is severe, the more will be the pathways affected leading to a large no. of cellular or tissue damage. The delta variant causes the pathways to be affected more than that of other variants.

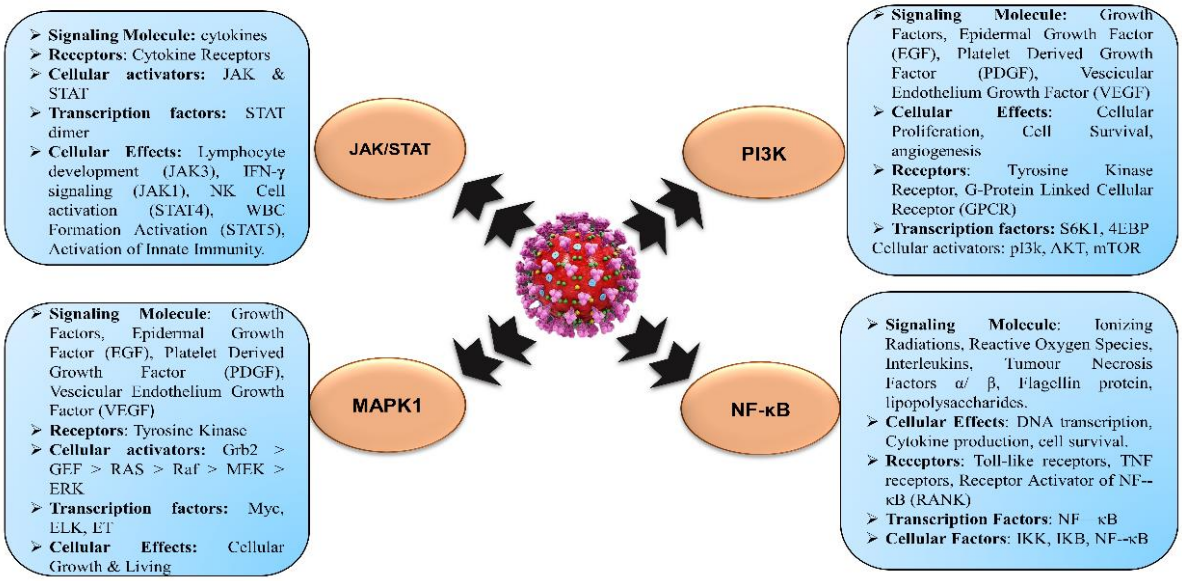

Figure 2. Major pathways affected due to Coronavirus infection

1. Janus Kinase/Signal Transducer and Activator of Transcription Proteins (JAK/STAT) signaling – The pathway is a network of protein complexes mainly associated with the events like immune defense, apoptosis and metastasis. The system transmits signal from chemoreceptors present outside the cell to the nucleus that triggers transcriptional activation of genes. The distorted signaling of JAK/STAT attributes to dermal illness, malignancies and immune dysfunction.

Interleukins (IL-6 & IL-1β) and Interferon-γ (IFN-γ) are the mediators that operate JAK/STAT Pathway. IL-6 instigates the gene expression of Angiotensin-II resulting in the increased level of IL-6 expression [46]. This pathway swiftly channelizes the signals outside the cell via interferons, hormones, cytokines and colony-stimulating factors (CSFs) that aids to switch the expression of genes by transcription factors of STAT [47]. This pathway is influenced by the following proteins that generate multiple immune responses.

i) 4 JAKs – JAK1, JAK2, JAK3 and TYK2

ii) 7 STATs – STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6.

Signaling molecule binds to the cytokine or chemokine receptors enabling the dimerization of receptors. The JAK proteins present in the receptors came closer and cross-phosphorylates each other. Then, JAK phosphorylates the cytoplasmic domain of the receptor by transferring its phosphate group to the tyrosine group present in it. The STAT protein available in the cytosolic membrane binds to the phosphorylated form of cytosolic domain exhibited by cytokine receptor. The STAT then gets dimerized forming hetero or homo dimer. The dimer then moves into the nucleus and binds to the specific promoter regions and initiates the transcription of genes [47].

The continuous activation of JAK/STAT pathway due to COVID-19 infection leads to overexpression of cellular activators resulting in hyperinflammation and Cytokine release. The activated state of immune system led to severe and lethal consequences of the disease [45].

2. Nuclear factor-κB (NF-κB) Signaling – NF-κB is a group of proteins that modulates expression of gene, secretion of cytokines and growth of a cell. It is present in most of the animal cell and concerned with physiological responses against cytokine mediators, contagious infections like COVID-19, ultraviolet light, activated low density lipoproteins and cellular stress.

The transcription factor NF-κB controls inflammatory responses that promotes the transcription of multiple genes generated by COVID-19 infection. The pathway is stimulated by the binding of antigens (reactive O_2 species, interleukins, TNFs or flagellin proteins) to the receptor molecules like Toll like receptors, receptor activators of NF-κB (RANK), TNF receptors. The phosphorylation and dimerization of receptors results in the phosphorylation of IKKβ and IKKα. These kinases are linked to the phosphorylation of IκB protein bound with NF-κB subunits (p65 and P50) resulting in proteolytic cleavage and ubiquitination. The p50/p65 dimers are then released to be transported inside nucleus and binds to specific sequences that mediate the transcription of NF-κB genes [48].

The elevated levels of TLR, TNF and RANK receptors lead to pro-inflammatory responses correlated with COVID-19 disease severity.

3. Phosphatidylinositol 3-kinases or Phosphoinositide 3-kinases (PI3K) Pathway **–** These are a group of signal transmitting enzymes that can initiate the phosphorylation of inositol ring in phosphatidylinositol. They participate in cellular events like cellular division, multiplication, diversification, movement, internal cell trafficking and malignant disorders.

PI3K-AKT-mTOR Pathway is regulated by the binding of growth factors such as EPGF, VEGF and Fibroblast growth factor to the transmembrane Receptor Tyrosine Kinase (RTK). This helps one of the receptors to get phosphorylated and then cross phosphorylate the other RTK. The entire RTK protein family is activated after the event of cross phosphorylation starting with the activation of PI3K protein. PI3K stimulate mTOR by basic cell signaling. S6K1 and 4EBP are the transcription factors activated by mTOR. The pathway regulates the cell growth, cell division and angiogenesis.

Elevated levels of platelet activation, thrombin, tissue factor and low fibrinogen count are detected in patients after the COVID-19 infection. GPCR, cytokines, Angiotensin II along with blood clotting factors are found to be elevated in infected patients leading to over expression of cells and formation of blood clots [49].

This pathway involves a cascade of kinases and phosphatases that interplay to cause various cellular responses. Proteomics based study have shown that SARS-CoV2 infection resulted in changes at various phosphorylation sites prominently which accounted to approximately equal to 12.5% of the approximate 12 000 screened sites [50].

4. Mitogen Activated Protein Kinase Pathway – The MAPK/ERK pathway is a protein network in the delivers a stimulus from receptors located on the cell surface to the genetic material. Several proteins like MAPKs formerly known as ERKs (Extracellular Signal-Regulated kinases) communicate by phosphorylating the adjacent protein to function as ON/OFF switches. Mitogen-activated protein kinases (MAPKs) regulate differentiation and multiplication of cell and programmed cell death. MAP Kinases present in mammals are linked to the 3 main kinase groups; p38 MAP Kinases or Stress-activated protein, kinases (SAPKs); Extracellular signal-regulated kinases (ERKs) and Jun amino-terminal kinases (JNKs).

The p38s MSPKs are interlinked with the viral infection of SARS-CoV-2. The p38 MAPK pathway is prompted by inflammatory mediators and biological stress that activates immune response and inflammation [51]. The p38 MAPK is subdivided into four proteins – p38α, p38β, p8γ and p38δ. These sub proteins are responsible for different gene expressions in tissues or cells. The p38α and p38β perform ubiquitination whereas p38γ and p38δ generates tissue-specific responses. The pathway comprises 3 major protein

kinases that are consecutively recruited sequentially preparing specific and diverse signaling mechanism [51].

The pathway is operated by multiple external stimuli such as growth factors (epidermal, platelet derived, vesicular endothelium), cellular stress, inflammatory cytokines, IL-1 and TGFβ. The major executive MAP3K such as Apoptosis signal-regulating kinase (ASK), Dual-leucine-zipper-bearing kinase (DLK), MAPK/ERK kinase (MEKK), Mixed-lineage kinase 3 (MLK3) and Transforming growth factor β-activated Kinase 1 (TAK1) are involved in procuring the inflammation [52].

Once, MAP3Ks gets phosphorylated energize MAP2Ks. MKK6 and MKK3 are the frequent MAP2Ks that activate p38 MAP Kinases whereas MKK3 is not able to activate p38β [48]. The p38 can phosphorylate various protein kinases –1) MAPK activated protein kinase 2 (MK2) 2) Transcription factors (p53, ATF1, ATF2 and ATF6).

The p38 can control the expression of genes transforming numerous surface receptors of cells and cytokines [53]. The p38 contribute to the post-transcriptional modification of TNF-α & inflammatory cytokines translation of IL-1β [54]. Hence, the regulation of p38 pathway elevates the production of pro-inflammatory mediators such as IL-1β, IL-6 and TNF-α that has a significant role in CRS leading to alveolar tissue damage, lung injury and respiratory disorders developed as a result of SARS-CoV-2 infection [52].

SARS-CoV-2 Transmission and Host Signaling

Viruses employ host mechanisms to generate a favorable host habitat during infection. About Ninety-seven cellular kinases were shown to be regulated by a phosphoproteomics investigation of SARS-CoV-2-infected Vero cells [7]. Some activated kinases such as guanosine monophosphate-dependent protein kinases engaged in p38-mediated signaling. Cell growth, cell cycle and cytoskeleton regulators have been downregulated. The Mitogen Activated Protein Kinase (MAPK1) pathway mitigates the excitation of inflammatory mediators such as CCL2, IL-6, CXCL8, TNF-α and CCL20 [7]. The extremely stimulated highly transcription factors such as c-Jun, NF-κB and monocyte enhancer factor-2C are the downhill of this pathway.

Interestingly, SARS-CoV-2 infection is substantially connected with cell cycle arrest at the S/G2 crossover, while M phase extension is negatively associated. During viral infection, S/G2 arrest may be triggered by a deregulation of cyclin-dependent kinase 2 (CDK2) activity [49]. SARS-CoV-2 infection generates an abnormal, delayed host immune response that promotes the replication of virus deprived of IFN-I & II reactions while conversely elicits efficient chemokine production [55]. Immunological investigations of SARS-CoV-2 infected patients suffering from various comorbidities revealed that NF-κB pathway is one of the major pathways that is affected resulting in most of the inflammatory responses [56].

TNF and IFN produce inflammatory cell damage and tissue disruption by significant interaction among various modalities of cell death, including apoptosis, pyroptosis, and necroptosis, collectively known as PANoptosis [57]. The transmitter and transcription regulator Janus Kinase (JAK/STAT1) or interferon regulatory factor-1 (IRF1) was reported to be regulated by a blend of TNF-α and IFN-γ leading to the generation of Nitric oxide (NO). This triggers PANoptosis effectuated by FADD (Fas-associated Death Domain Protein) and Caspase-8. The increased levels of TNF-α and IFN-γ generate cytokines storm in a mice infected with COVID-19 but can be treated with stabilized antibodies against the TNF and IFN signaling molecules. This shows the clinical importance of cytokine directed cellular damage transduction pathways [58]. An in-depth study of these signaling pathways in clinical samples of SARS-CoV-2 infection using additional experimental approaches will certainly lay a strong foundation for drug discovery (Figure 2) [59-60].

RESULTS

In-depth study of the literature focused on different variants of SARS-CoV-2 and the pathways affected due to infection is comprehensively consolidated in this review. The various web portals of National and International agencies, research and review articles were consulted for this study. It is an established fact that SARS-CoV-2 is a lethal and dangerous virus among the SARS family of viruses. Development of frequent mutations in the virus genome is responsible for the evolution of new variants which are more pathogenic than the parent one. The mechanism of viral attack/replication, virulence ability, pathogenicity and implication of SARS-CoV-2 affects many organs or tissues that has been summarized in this review. The variants of SARS-CoV-2 are linked to the deregulation of signaling pathways. Virus-mediated modulation of essential signaling pathways such as NF-κB, JAK-STAT, MAPK/ERK and PI3K triggers the cytokine storm activity that seems to be the prime cause of tissue damage. Cytokine storm leads to activation of inflammatory responses or the innate immune responses. The continuous activation of the signaling pathways lead to the formation

of malignancy or the impairment of normal cells. The omicron and delta strains were highly transmissible and infective.

DISCUSSION

The RNA viruses particularly single-stranded RNA (ssRNA) like SARS-CoV2, undergoes higher mutation as compared to the DNA viruses thus enhancing its virulence, infectivity, and transmissibility [61]. SARS-CoV-2 is a disastrous virus that has caused the pandemic since past three years. The virus consists of structural genes like S, E, N, M and various non-structural proteins such as NSPs 4-16, ORF7, ORF3 and ORF6). The S gene allows the virus to penetrate inside the host system by integrating with ACE receptors and TMPRSS2 [9]. The non-structural proteins are involved in the molecular replicating events [18]. The data that was published earlier was reviewed thoroughly to design the study on understanding the effect of SARS-CoV-2 variants on major signalling pathways that results in comorbidities and hyper-inflammatory responses [43]. These variants are categorized as VOCs (alpha, beta, gamma, delta and omicron) and VOIs (epsilon, zeta, eta, iota, theta, kappa, lambda, mu) depending upon their transmission and infectivity rates. The variants exhibit mutations in receptor binding domains, N-terminal domains and ORF regions [33]. The track record of variants was curated from the web links of several platforms like WHO, Nexstrain clade, CDC, GISAID clade.

SARS-CoV-2 requires a suitable environment for replication. It affects the host system by cell invasion and transcriptional modulation of viral proteins [33]. Several studies have proposed the effect of the SARS-CoV-2 infection on the signaling pathways which we have tried to integrate in this review. The major pathways that could be potentially affected due to SARS-CoV-2 infection are MAPK/ERK, PI3K, JAK/STAT, NF-κB. The viral infection leads to the activation of various signaling molecules like ILs, TLR, TNF-α, IFNs, blood clotting factors, GPCR (G-Protein Coupled Receptors) etc [43]. These molecules produce pro-inflammatory responses leading to generation of cytokine storms or tissue damage [44].

The present review is an attempt to showcase the transmission rates of delta and omicron variants were high but the infectivity rates of delta were more than that of omicron (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/). All the variants of SARS-CoV-2 are associated with several symptoms in patients like sore throat, fever, dizziness, sneeze and cough [62]. The variants are mainly linked with the signaling of JAK/STAT, PI3K, NF- KB and MAPK1 pathways. The delta and omicron are more transmissible among all the other variants. The delta variant is more infective as compared to the omicron [30].

CONCLUSION

All the reported cases collectively conclude that the infectivity and transmissibility is the outcome of the SARS-CoV-2 effect on the host signaling pathways. This also corelates to the hyper-activation of innate immunity and development of comorbidities causing severity among infected population. The delta and omicron variants more efficiently dysregulate the signaling pathways with the delta variant being considered as more disastrous than omicron resulting in large number of infections and deaths. However, the molecular basis of SARS-CoV-2 infection on signaling pathways still remains a subject of scientific exploration.

Funding: GM acknowledges the extramural funding support from Indian Council of Medical Research (ICMR) (Project Id: 2021-6466).
Acknowledgments: GM thanks National Institute of Biological, Noida for infrastructural support.
Conflicts of Interest: The authors declare no conflict of interest.

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