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Review Article

TRINITY OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2: ORIGIN, GENOTYPE, PHENOTYPE, AND IMMUNE RESPONSE IN CORONAVIRUS DISEASE-2019

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ABSTRACT

The coronavirus disease-2019 (COVID-19) outbreak by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or a novel coronavirus (2019-CoV) has prompted global health concerns. A pandemic resulted from the disease's transmission through many routes. In this pandemic, the interaction between coronavirus and the host immune system, particularly the innate immune system, is becoming more prominent. Against viruses and pathogens, innate immunity serves as a first line of defense. Our understanding of pathogenesis will benefit from a better grasp of the mechanisms of immune evasion techniques. The origin, classification, structure, and method of transmission of SARS-CoV-2 were summarized in this paper. We have discussed the importance of important communications. In this review, we have discussed the function of important components of the innate immune system in COVID-19 infection, as well as how the virus evades innate immunity through multiple tactics and contributes to a wide range of clinical symptoms and outcomes.

Keywords: Severe acute respiratory syndrome coronavirus-2; Coronavirus disease-2019, Genomic Origin, Pathogenesis, Immunity.

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INTRODUCTION

The outbreak of new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) — the causal agent of Coronavirus disease 2019 (COVID-19) – began in Wuhan, Hubei Province, China, in December 2019, and quickly spread throughout the country. COVID-19 was declared a global pandemic by the World Health Organization on March 11, 2020. Fever, dry cough, dyspnea, rhinorrhea, sneezing, sore throat, confusions, chills, muscle, chest pain, hemoptysis, pyrexia, acute respiratory distress, and diarrhea with nausea and vomiting are all possible symptoms, but they are less prevalent [1,59]. COVID-19 can cause mild MERS-CoV to severe SARS-CoV sickness, which can lead to hospitalization and intensive care unit admission and increased mortality among elder adults [58]. The International committee on taxonomy of viruses ICTV has named novel coronavirus (2019-Nov) as SARS-CoV-2 and the disease it causes is called COVID-19 [2]. SARS- CoV- 2 is the 7th identified human coronavirus and 3rd novel one to emerge in the past 20 years [60].

THE SARS-COV2: CLASSIFICATION AND ORIGIN

Coronaviruses are enclosed, single-stranded, and positive sense RNA viruses belonging to the Coronaviridae family of the Nidovirales order. Letovirinae and Orthocoronavirinae are two subfamilies of the Coronaviridae family. Alphavirus belongs to the Letovirinae family, while Alphacoronavirus, Betacoronavirus, Gamma Coronavirus, and Deltacoronavirus belong to the Orthocoronavirinae family (Fig. 1).

The human viruses HCoV-229E and HCoV-NL63 belong to the Alphacoronavirus genus. Mouse hepatitis virus (MHV) prototype, three human viruses (HCoV-oc43, SARS-HCoV, and HCoV-HKU1), and MERS-CoV are all members of the Betacoronavirus genus. Cetacean and bird viruses belong to the Gamma Coronavirus genus; the Deltacoronavirus belongs to the Deltacoron genus contains virus of pigs and birds [4-6].

ORIGIN

The novel coronavirus originated from the Hunan seafood market, Wuhan, China. SARS-CoV-2 genomes were sequenced and suggested that it might have also originated from bats but, still the zoonotic source for the spread of virus is not known. According to the phylogenetic tree, SARS-Cov-2 is closer to SARS-like bat coronaviruses, (CoVsZxC21and ZC45). Thus, this SARS-CoV-2 belongs to Betacoronavirus Subgenus sabecovirus [7]. Among the four genera of coronaviruses, alphacoronavirus and betacoronavirus can infect mammals while gamma coronaviruses and delta coronavirus tend to infect birds, six coronaviruses have been identified as human susceptible viruses, among which alpha coronaviruses: HCoV-229E and HCOV-NL63 and Betacoronavirus- HCoV-229E and HCov-NL63, and Betacoronavirus HCoV-HKU1 and HCoV-OC43 with low pathogenicity, cause mild respiratory symptoms similar to a common cold, respectively. The other two known Betacoornavirus, Sars-CoV and MERS-Cov lead to severe and potentially total respiratory tract infections [10].

TRANSMISSION

COVID-19 infection transmission was first classified as zoonotic (transmission of infection from animal to human). Later, it was suggested that human-to-human transmission was the primary mechanism of transmission for the present pandemic. Horizontal transmission through direct touch, aerosol transmission (viruses remain alive on at least 3 h in aerosol and 48–72 h on materials such as stainless steel and plastic surfaces), and droplet transmission are all examples of human-to-human transfer (Fig. 2). Personal protective equipment can be used to prevent (b) fecal-oral transmission, (c) vertical transmission, and (d) nosocomial transmission of COVID-19 from patients to health care personnel vertical transmission and (d) nosocomial transmission of COVID-19 from patients to healthcare workers can be controlled using personal protective equipment. Fomites are the principal source of infectious particles through indirect contact [8]. The most harmful mode of COVID-19 transfer among HCWs is droplet mode transmission [9].

GENOTYPIC AND PHENOTYPIC CHARACTERISTICS OF SARS-COV2

Genotype

SARS-CoV2 is an enclosed, non-segmented, single-stranded, positive-sense RNA virus with a diameter of 60–120 nm [11,12], a size of roughly 29.9kb, and a nucleoprotein within a capsid. Matrix protein makes up the nucleoprotein. It features a helical symmetry

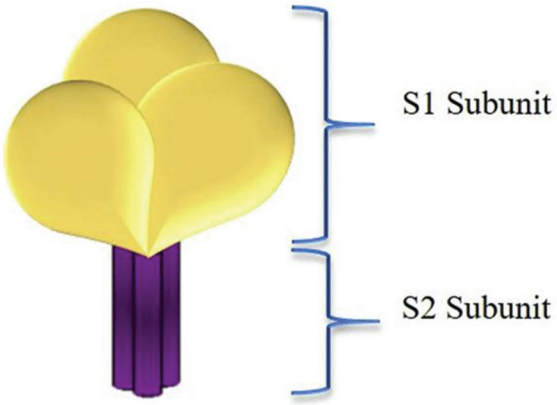
nucleocapsid and a lipid sheath produced from the previously infected host's membrane. Glycoprotein projections in the shape of clubs can be found on the envelope (Fig. 4). Coronaviruses have the biggest genomes (ranging from 26.4 to 37.1 kb) of all known RNA viruses, with G and C content ranging from 32 to 43% [13]. With a genome size of 29,891 nucleotides and 9860 amino acids, SARS-CoV2 contains a G and C of 38% [7].

The genome of coronavirus has a variable number of open reading frames (ORFs), ranging from 6 to 11. [10]. With seven ORFs, SARS-CoV-2 RNA is 5'caped and 3' polyadenylated [11]. ORF 1a and 1b make up two-thirds of the viral genome, encoding 16 non-structural proteins and translating two polyproteins, pp1a and pp1ab (NSP). The remaining ORFs code for structural proteins such as spike(s) protein, Envelope protein (E), Membrane protein (M), Nucleocapsid protein (N), and a few auxiliary proteins [10,11]. The coronavirus sgRNA is used to translate all structural and auxiliary proteins. ORF 10 and 11 of the 1/3rd genome, located near the 3›terminus, encode these proteins [13]. In addition, in some cases, the hemagglutinin esterase (HE) gene is located between ORF1b and ORF S [11,12,14,15].

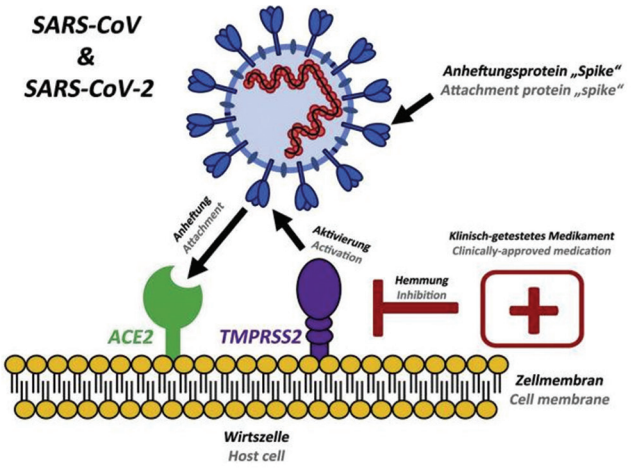
PHENOTYPE

The membrane of the coronaviruses has 3 or 4 viral proteins.

Spike glycoprotein (S)



The coronavirus has spike-like protruding projections on its surface called large surface glycoproteins or spike (S) protein [16,17]. The S-protein plays a significant role in pathogenesis by binding to the host cell. It acts as a Type-I membrane glycoprotein with single channel peptide, responsible for host receptor binding, viral entry and with most variable sequencing in coronavirus genomes [17]. It consists of an ectodomain element, transmembrane moiety, and a short intracellular C fragment. Its molecular weight is about 141178KDa and contains 1273 amino acids [16]. S1, S2, and S2' are three subunits (Fig. 3). Through RBD, the S subunit is responsible for binding to the cell receptor (receptor binding domain). The SARS-CoV-2 S1 subunit enters the cell through the angiotensin-converting enzyme 2 (ACE-2) host receptor. The lung, heart, ileum, kidney, and bladder all have higher levels of ACE 2. The S protein undergoes structural changes as it enters the endosomes of the host cells throughout this process. The S2 subunit functions as a fusion protein that aids in virion-cell membrane fusion. The s-protein is broken into S1 and S2 subunits by protease after binding to the S1/S2 cleavage site. Another protease, such as transmembrane protease serine, can also cleave it.



Nucleocapsid protein (N)

The viral RNA is packaged inside the ribonucleocapsid by the nucleocapsid protein. The N-protein is the only protein found in nucleocapsids, and it is expressed in the host sample during infection's early stages. The nucleocapsid N protein is a highly conserved portion of CoV that is 90% similar to SARS-CoV. It is a one-of-a-kind construct with a serine (SR)-rich linker region sandwiched between N- and C-terminal domains. It connects the viral DNA to a bead pattern on a thread [16,18].

Envelope protein (E)

CoV-2 E Protein has a molecular weight of 8–12 kDa and contains 75 amino acids. It is a transmembrane protein containing an ectodomain at the N-terminus, a hydrophobic domain at the C-terminus, and an endodomain at the C-terminus that acts as an ion channel. This architecture encourages the virus to assemble and release itself [16]. SARS-CoV replication does not require it, but pathogenesis does involves with this protein [16,19,20].

Membrane protein (M)

M-protein is the most abundant protein in coronaviruses, and it is responsible for the virus's unique shape. It is a 30kDa structure with three transmembrane domains, a short glycosylated N-terminal ectodomain, and a very big C-terminal endodomain. It is in charge of RNA packaging [14,16].

Viral Receptors

The primary indication of coronavirus host spectrum and tissue tropism is receptor attachment. Cell surface factors such as amine-peptidase N for HCoV 229E, ACE-2 for SARS and SARS-CoV2, dipeptidyl peptidase 4 for MERS CoV, and O-acetylated sialic acid for HCoV-oC43 serve as receptors. With the help of host proteases, the spike protein was activated. The endosomal cysteine protease cathepsins L and the trypsin-like serine protease trypsin-like serine protease trypsin-like serine protease trypsin-like serine protease trypsin-like serine protease trypsin [21].

INNATE IMMUNITY

Innate immunity is the first line of defense (non-specific) against infections, with an antigen-independent defense mechanism and no immunologic memory. The innate immune system is critical for recognizing and eliminating contaminated cells during viral infections, as well as organizing an adaptive immune response. Anatomic, physiologic, endocyclic and phagocytic, and inflammatory barriers are among the four defensive barriers [25,26]. Macrophages, dendritic cells, mast cells, neutrophils, eosinophils, and natural killer cells play a role in innate immunity in both hematopoietic and non-hematopoietic cells. Its responsiveness is a feature of epithelial cells of the skin, respiratory tract epithelial cells, and IT cells, and the genitourinary tract.

During viral infections, the innate immune system is crucial for identifying and removing infected cells while also coordinating an adaptive immune response. To detect and defend rapidly against various microbes, mammalian hosts have evolved multiple pattern-recognition receptors (PRRs) including Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), the nucleotide-binding oligomerization domain –like receptor family proteins (NLRs), and absent in melanoma 2 (AIM2). In response to specific pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), some PRRs, particularly members of the NLR family and AIM2, have the ability to assemble a large multiprotein complex called the inflammasome [69]. Some PRRs, particularly those in the NLR family and AIM2, have the ability to form the inflammasome, a massive multiprotein complex [69] PAMPs are highly conserved pathogen products that should be detected by a collection of non-clonal germline-encoded receptors with broad specificity [27,28]. The inflammasome causes membrane hole development and pro-inflammatory cytokine processing when it is assembled, resulting in pyroptosis, a type of inflammatory cell death [69] The cell's own endosomal and cytosolic PRRs identify pathogen nucleic acids. DAMPs from injured cells can also activate PPRs from damaged cells [29,30]. These RNA sensors start a signaling cascade in innate immunity against respiratory viruses when PAMPs are recognized by endosomal receptors (TLR 3,7,8) and cytosolic receptors (MDA5 and RIG-I). NFKB, IRF3, IRF7, and other transcription factors are activated as a result of this signaling pathway. Type I and type III interferons, as well as other pro-inflammatory cytokines and chemokines, are stimulated by these stimuli [31,27].

Interferons (IFNs) activate the IFN effector response through the JAK/SAT pathway, which results in the activation of Interferon-stimulated genes (ISGs) in infected and nearby cells. Type-III IFN has been discovered to be the first line of defense against respiratory viruses, and it does not cause significant inflammatory reactions [27]. During viral infection, innate immune signaling and inflammasome activation are well-known and important barriers. Excessive stimulation of the innate immune system, on the other hand, can lead to systemic inflammation and tissue damage, both of which are harmful to the host. A wide spectrum of viral illnesses causes systemic hyperinflammation [67].

INNATE IMMUNE RECOGNITION IN SARS-COV-2

When coronaviruses, such as SARS-CoV-2, come into touch with the respiratory mucosa, they try to enter the cells through host receptors such ACEs and envelope anchored S-glycoproteins [32]. The identification of S by membrane associated TLR2 through stimulation of the nuclear factor kB (NFkB) cascade in epithelial cells, monocytes, and macrophages can start the innate immune reaction signaling [22]. When a virus enters the cell, its ssRNA enters the endosome lumen and activates intracellular TLRs, primarily TLR7/8 [23]. Viruses subsequently reproduce rapidly within alveolar epithelial cells [24] and secondary structures with dsRNA domains are detected by a different form of cytosolic PRR, such as MDA5 or PKR, which, in turn, stimulate antiviral gene expression [25].

Through the IRF 3/7 and NF kB pathways, TLR and RLR stimulate transcription factors necessary for the generation of IFN I and pro-inflammatory cytokines. SARS-CoV2 can also enter through CD147; however, the mechanism and receptor binding motifs are unknown [33]. It begins to transcript its genomic RNA and generates structural and non-structural proteins after obtaining entry to the cell. It proliferates without being identified by the host's innate immune response in the early days following infection by overpowering it. After a large number of cells have been infected, the symptoms begin with a high temperature and broad malaise [29].

Around 7 days following the onset of symptoms, the virus is either eliminated by the immune system, resulting in the patient's recovery; or the virus moves into the lungs (particularly by type-2 pneumocytes) and into the systemic circulation, causing endothelial degradation and oxidative stress. In roughly 3–5% of all patients, an exaggerated immune response leads to a "cytokine storm" in the 2nd week, with IL-6 activating macrophages, monocytes, and T-cells. The importance of innate immunity in the outcome of COVID-199 infections cannot be overstated [32,61].

INNATE IMMUNE EVASION MECHANISMS

SARSCoV2 uses immune blunting, or delay, techniques to get beyond the host's antiviral defenses, allowing for fast replication 33 or an intensification of the inflammatory response. 34 Virulence factors can mediate virus adhesion to epithelial cells via S protein, enhance virus dissemination through intercellular spaces through invasive enzymes, or provide resistance to host defense systems such IFN, NK cytotoxicity, and inflammatory response. SARSCoV2 has recently been discovered to share numerous structural and NS proteins with other coronaviruses, primarily SARSCoV (Figs. 5,6).

KEY COMPONENTS OF INNATE IMMUNITY IN COVID-19

Viral sensing PRRs

The most proximal event in the triggering and amplification of the innate immune response is the recognition of PAMPs and DAMPs [34]. The network of PRRs and accompanying signaling pathways is an important part of the innate immune system [35]. PRRs are germline-encoded receptors located on all immune-responsive cells. CD14, a membrane and soluble protein (mCD14, sCD14) that acts as a PRR and enhances the activation of TLR2, TLR3, and TLR4 by bacterial, viral, and host-derived products, serves as a PRR. These proteins significantly boost the inflammatory response generated by PRR [34].

TLRS

TLRs are proteins that play a role in the innate immune system's development and activation. PAMPs are recognized by a family of 11 Transmembrane receptor proteins [3]. TLRs are membrane-spanning type I receptors containing extracellular leucine-rich repeats for ligand binding, a transmembrane domain, and a Toll-interleukin-1 receptor resistance (TIR) domain in the cytoplasmic tails to activate intracellular signaling [35]. These sensor proteins are involved in both "self" and "non-self" situations. It recognizes a conserved microbial domain that works as a ligand for elements such as lipids, lipoproteins, proteins, RNA, and DNA. These microbial domains are called the PAMP [36].

These receptors are classified based on whether they are expressed intracellularly or extracellularly. Intracellular receptors on the cell surface are engaged in the detection of bacterial products, while extracellular receptors expressed in endosomes are involved in nucleic acid detection. TLR3, TLR7, TLR8, and TLR9 are endosomes. TLR3 recognizes double-stranded RNA, while TLR7 and TLR8 recognize single-stranded RNA. TLR9 recognizes hypomethylated CPG DNA [37].

It is abundant in dendritic cells, the placenta, and the pancreas [3]. TLR signaling is mediated by the TIR (Toll/IL-1 receptor) domain, which contains an adaptor molecule such as myeloid differentiation primary response gene 88 (MyD88), TIR-domain containing adaptor protein, or TIR-Domain containing adaptor inducing interferon Beta (TIR-Domain containing adaptor inducing interferon Beta) (TRIF) [38,39]. The TIR complex is involved in the generation of pro-inflammatory cytokines, type-I interferon, and the upregulation of costimulatory molecules during the inflammatory immune response [36].

Complement system

Inactive precursors of a group of proteins provide a protective effect against germs and viruses. There are three distinct pathways: Classic, alternative, and lectin, each of which activates different immune system components [3]. It acts as a catalyst for pro-inflammatory reactions [40]. It serves as a link between the innate and adaptive immune systems. It detects non-self-structures and activates zymogens through proteolytic cascades, leading to inflammation, opsonization, and cell lyrics [36].

Overactivation of complement may result in increased neutrophil and monocyte infiltration of the alveolar air sac as a result of excessive C3a and C5a production [42].

Collateral lung injury and aggravating variables for SARS-Cov-associated ARDs result as a result of this. SARS-Cov2 is a respiratory disease, and the predominant antibody generated is IgA, which, unless based on an aggregated antibody, is not dependable for activation of the conventional complement system [36]. Instead, the virus might be from IgA complexes or SARS-Cov. S-N glycan (N-330)MBL binding stimulates the lectin complement pathway, which protects mucosal immunity from invading viruses [41]. C3a products of the complement cascade aggravate SARS-Cov related ARDs in SARS-Cov2, whereas C5a causes inflammatory cell activation and cytokine release in SARS-Cov2. Degranulation of epithelial cells occurs as a result of this, and the number of epithelial cells increases vascular permeability, large number of inflammatory infiltrates, fluid and blood cells shift to alveoli, and lung pleura results in dyspnea and respiratory insufficiency [43].

Monocytes and macrophages

Mononuclear phagocyte systems present throughout the body. Monocyte-derived macrophages are the main generators of inflammation in COVID-19. These phagocytes have a wide range of plasma membranes and intracellular receptors [44]. In early infection, the occurrence of common symptoms due to the indirect result of epithelial cell necrosis by viral infection was mediated by ACE2 and other co-receptors such as transmembrane protease serine2. (TMPRSS2) phagocytosis of virus or epithelial cell debris by lung macrophage canactivate inflammasome by P2Rx7 and release IL-1Beta, type-1IFN, IL-6, and TNF [44,62]. The inflammasome is a multiprotein complex, which is the part of the innate immune system responsible for the activation of inflammatory responses [3]. Activated Inflammasome, recruits pro-caspase-1(Proteolytic enzyme), which activates pro-inflammatory cytokines such as pro-IL-1 B and pro-IL-18 by cleaving it. This leads to programmed cell death called pyroptosis [3]. IL-18 stimulates the production of IFN-γ, which determines the development of TH1 results in adaptive immunity development [45]. IL-1 released by macrophages through inflammasome contributes to cytokine storms responsible for a most aggressive form of COVID-19 [3].

Neutrophils

In COVID-19, the CBC profile was found to observe an increase in Neutrophil with lymphopenia. These cells may contribute to the healing process through virus clearance and production of growth factors for healing and reepithelialization of damaged regions of the lungs [3]. In SARS-Cov2 respiratory epithelium, infections result in cell secretions of multiple cytokines, chemokines, and DAMPs which facilitates the PMN recruitment to the site of infection [46]. Viral infection can induce the release of neutrophil extracellular traps (NETs) by neutrophils NETs are known to immunize and degrade bacteria, fungi, and viruses [46]. NETs released neutrophil contributes to organ damage and mortality in COVID-19 patients [47]. Net comprises extracellular DNA fibers, histones, microbiological proteins proteases such as neutrophil elastase, and oxidant enzymes such as myeloperoxidase, which are released by neutrophils at the time of infection [47]. This process is called NETosis and plays a role in controlling pathogens but also has detrimental effects on cardiovascular and pulmonary disease. Mitosis in COVID-19 infection has a role in vascular complications, where thrombotic disease can drive organ damage [48]. High levels of IL-6 observed in COVID-19 patients induce NETs. Additional triggers of NETosis include viral-damaged epithelial cells, activated endothelial cells, activated platelets, and inflammatory cytokines like IL_1β [47].

NK CELLS

Essential in control of viral infections and functional impairment of NK cells correlates with the persistence of SARS-Cov2. In COVID-19 patients, Nk Cells were found to be reduced [33]. The plasma membrane of NK cells along with CD16 it also has killer immunoglobulin-like receptors (KIRs) which have crucial roles in NK cells, licensing, and their subsequent cytotoxic functions [33]. In peripheral blood of COVID-19 patients, the expression of KIRs and C16 in NK cells was significantly decreased, suggesting impaired maturation of NK cells or migration of circulating NK cells into the peripheral tissues of SARS-CoV2 patients [50]. Cytokines like IL-12 secreted by Macrophages and dendritic cells promote NK cell proliferation, cytotoxicity, survival, and IFN-γ production. IFNλ mediated IL-12 production suggests that early production of IFN-γ and Nk-cell stimulation may act to limit SARS-CoV2 infection [47].

In SARS-CoV-2 patients, the NK cells are functionally exhausted due to increased expressions of anNk inhibitory receptor called NKG2A and decreased expression of CD107a, IFn-γ, Il-2, and Granzyme B in NK cells [51]. There is also upregulated expression of the genes which encoding inhibitory receptors including TIM3 and LAG3 in NK cells from COVID-19 patients. While, Nk cells members and activity appears to be diminished in COVID-19 patients remains unelucidated. [47].

Dendritic cells

Dendritic cells are a diverse group of antigen-presenting cells that are widely distributed in the respiratory tract. These are two main categories of dendritic cells are plasmacytoid and conventional dendritic cells. In the early phase of infection almost all immune and non-immune cells produce IFN-I α/β in response to viral infectious plasmacytoid dendritic cells are considered as the main source of IFN-1 which is essential for the protection of the host; by promotes the removal of virus from the circulation by macrophage and also be the reason for individuals with non-severe COVID-19 [52]. SARS-CoV2 infects Dcs among other cells which significantly contribute both innate and adaptive immunity. Dc has a peculiar characteristic of being able to enhance or suppress the immune system. Dc-specific molecular non-integrin three adherent (DC-SIGN, CD 209) is a member of superfamily receptor of type C lectin that highly expressed on dc surface. This receptor allows interacting with both the pathogens and endothelial epithelial and myeloid cells. The binding requires mannose residues on the pathogen [53]. In acute SARS-CoV2 patients, the conventional DC's (CD11c+) were significantly reduced than in the convalescent phase. The percentage of PDC (CD123) was also reduced although not significantly in both convalescent and acute patients. The ratio of CD11c+:CD123+ was higher in the acute phase, especially in severe cases. These findings suggest that SARS-CoV2 has cytopathic effects on dendritic cells [52]. Immature dendritic cells are turned as mature after antigen-capture which produces a wide variety of cytokines including IL-2, IL-1 β, IFN-α, β, γ, IL-4,10, and TNF α [52]. The capacity of Dcs to stimulate T cells depends on its maturation state, thus production infection of immature dendritic cells may delay the activation of T-cells Thus, the inability of dc to provide the switch from innate to adaptive immunity may be important for COVID-19 pathogenesis [52].

Interferon and cytokines

Interferon is signaling proteins involved in innate and adaptive immune responses, with an important role in the inhibition of viral replication through different effector proteins [3]. There are three types of IFN- type I (IFN- α, β), are largest IFN family includes IFN α (13 subtypes) encoded at chromosome 9,IFN β encoded at chromosome- 12; type II (IFN γ), and type III (IFN λ [3,36]. All three are involved in coronavirus infection [3]. Almost all types of cells are capable of producing IFN- α/β; pDCisa specialist in Type I IFN producing cells, particularly producing α, β, ω during the course of infection [36]. In the early stage of infection, type I has a predominant role, production is enhanced by viral RNAs through 2 cytosolic proteins: RIG-I and MDA5. This recognition of viral RNA leads to activation of IRF3 which determines the initiation of transcription of type I IFN [3,54]. SARS-CoV2 has several proteins including nsp1, nsp3, nsp16, ORF 3b, ORF6, and M and N proteins which act on the type I IFN pathway either by inhibiting the transcription or by acting on effector mechanisms. It was observed a peak in IFN α2 production after 8-10 days of symptoms onset. Also observed in the ICU patients, the IFN-1 production was suppressed [3]. IFN- λ is present in lower airways in COVID-19 patient mediates antiproliferative

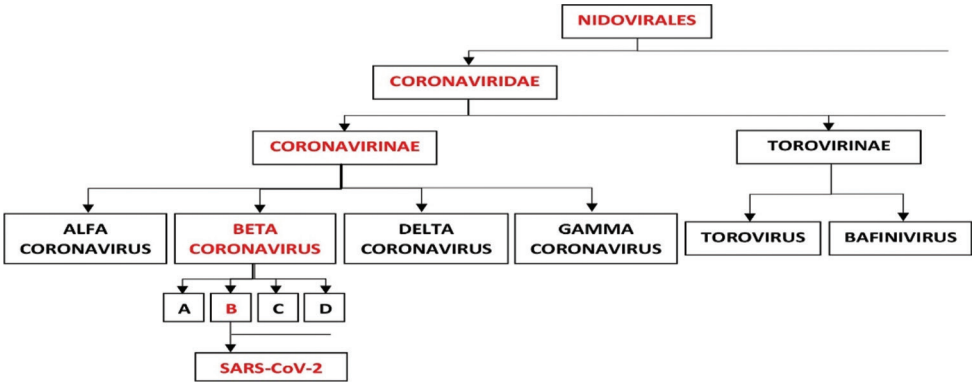


Fig. 1: Classification of SARS-CoV-2

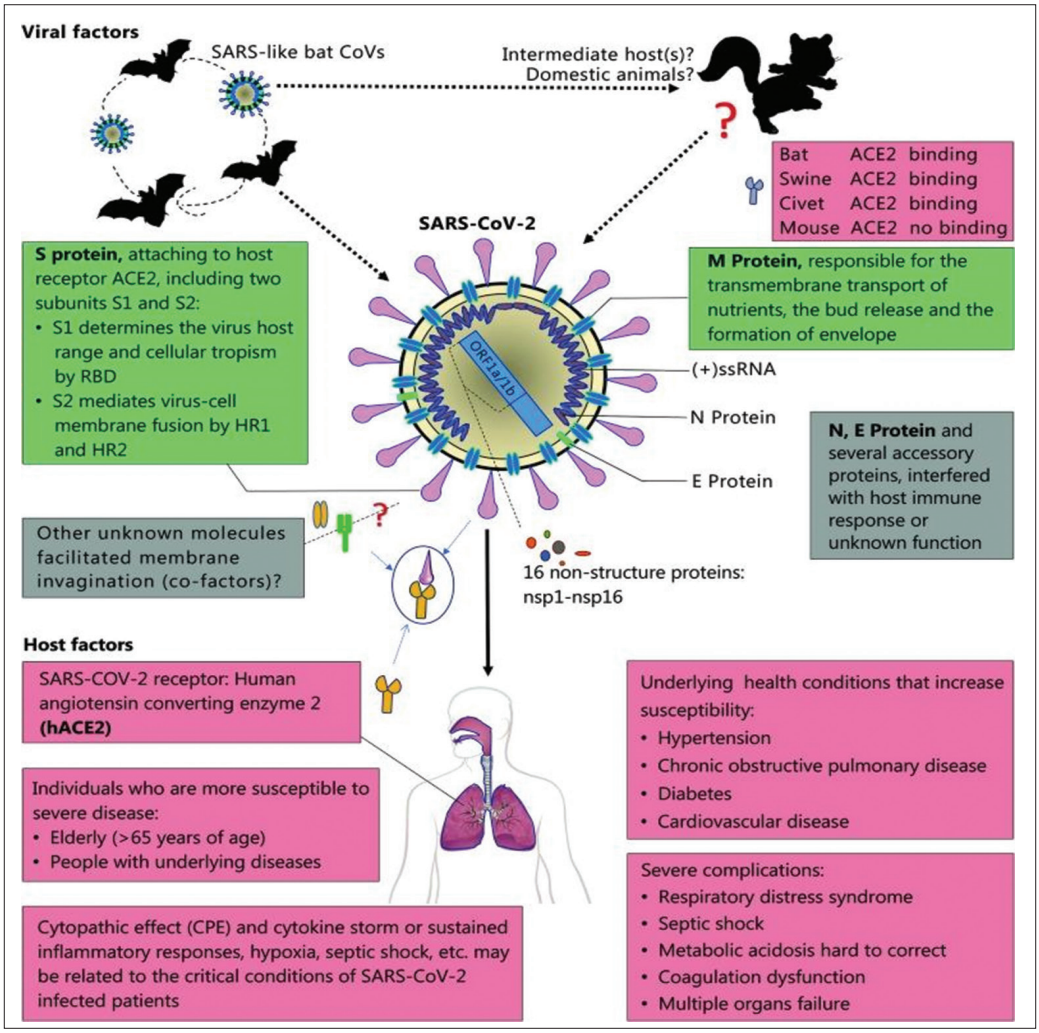


Fig. 2: Modes of transmission of SARS-CoV-2

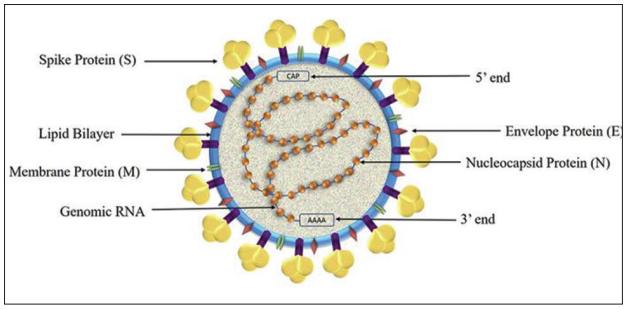


Fig. 3: Schematic representation of SARS-CoV-2 structure

effects during repair of the lung epithelium, this effect occurs through p53 induction [47]. Type-I IFNs bind to the transmembrane receptor, IFNAR, composed of IFNAr1 and IFNAR2, these lead to activation of the intracellular signaling pathway JAK/STAT which initiates transcription of ISGS [49,55].

Cytokines

COVID-19 patients experience a "cytokine storm" that drives much of the pathophysiology of the disease. In SARS-CoV-2 patients, there will be an increase in both pro-inflammatory and anti-inflammatory circulating cytokines [56,47]. The pro-inflammatory cytokines including G-CSF, TNF α, MCP 1, IL-10, IL-2, IL-7, and IL-1 β were

Fig. 4: Representation of 5′ capped mRNA has a leader sequence (LS), poly-A tail at 3′ end, and 5′ and 3′ UTR. It consists of ORF1a, ORF1b, Spike (S), ORF3a, Envelope (E), Membrane (M), ORF6, ORF7a, ORF7b, ORF8, Nucleocapsid (N), and ORF10 Rrp

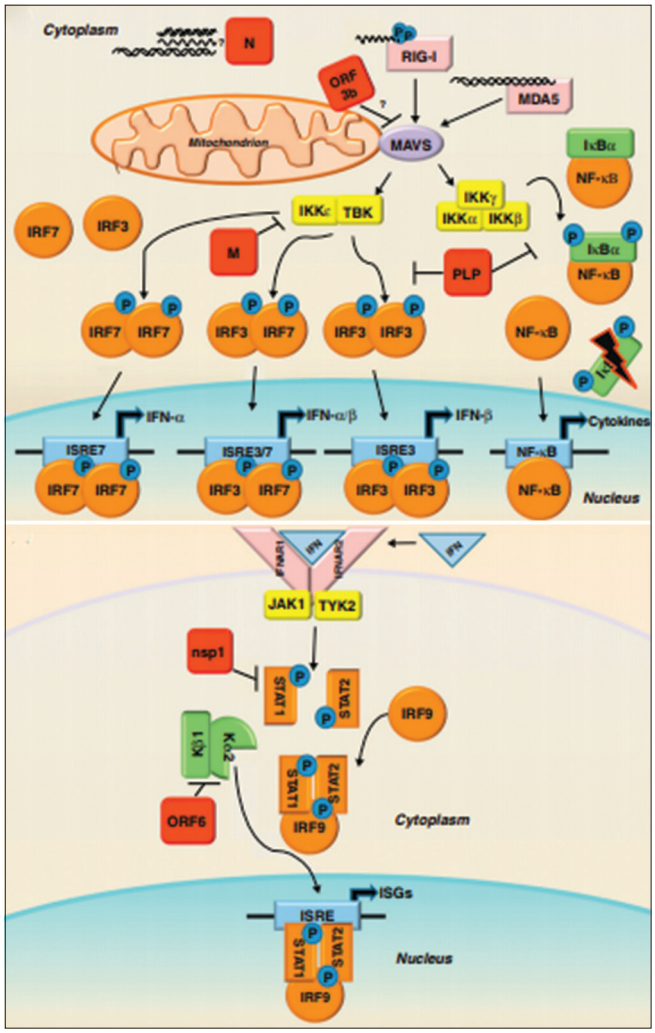


Fig. 5: (a) RLR family of innate immune receptors induce Type I interferon. The family of RIG-I Like Receptors (RLRs) contains three cytosolic RNA helicases that recognize non-self RNA species resulting from viral replication [93]. The two signaling sensors within the RLR family are RIG-I and melanoma differentiation associated factor 5 (MDA5). The third RLR, laboratory of genetics and physiology 2 (LGP2, not shown), facilitates recognition of viral PAMPs by RIG-I and MDA5, but is dispensable for their signaling [94]. RIG-I recognizes primarily 50 ppp-RNA molecules with secondary motifs of dsRNA or ssRNA of short length [95,96]. MDA5 recognizes longer dsRNA motifs than RIG-I [97]. Following binding of viral RNAs, RIG-I and MDA5 interact with the mitochondrial membrane bound adaptor molecule MAVS (mitochondrial antiviral signaling protein, also referred to as IPS-1, VISA, or CARDIF) to transduce the signal through complexes of kinases: the IKKe/TBK1 complex and the IKKa/IKKb/IKKg complex. The IKKe/TBK1 kinases phosphorylate the transcription factors IRF3 and IRF7, which then form homodimers or heterodimers. On dimerization, the transcription factors enter the nucleus to initiate transcription of Type I IFNs (IFN-a and IFN-(b). While IRF3 is nearly ubiquitously expressed in cells, IRF7 is an ISG typically expressed at low levels, so it is thought that IRF3 mediates transcription of the majority of early IFN expression

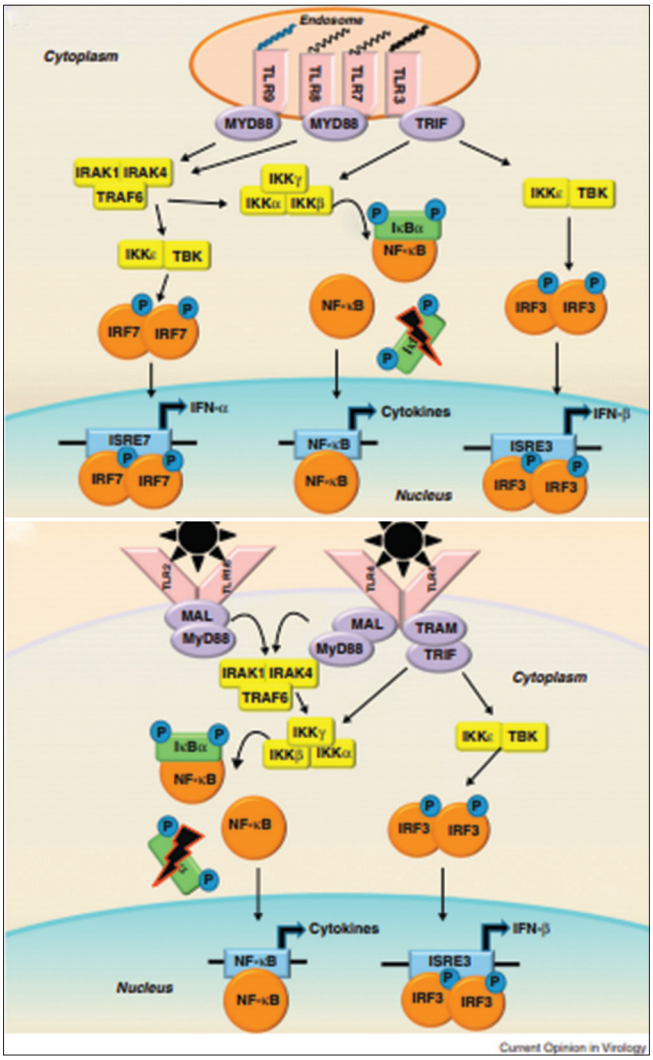


Fig. 6: Pathogen associated molecular pattern sensing by TLRs. (a) In the endosomal compartment, TLRs recognize viral nucleic acid PAMPs: TLR3 recognizes dsRNAs, TLR7/8 recognizes ssRNAs, and TLR9 recognizes CpG DNA motifs. (b) On the surface of cells, TLR2 and TLR4 are known to recognize viral glycoproteins [47,99]. TLR2/6 heterodimers help to activate the innate immune response to RSV, though the viral PAMP recognized has not been determined [100]. TLR1/2 heterodimers have been shown to recognize viral glycoproteins, though their potential role in respiratory virus infection has not been determined [99]. While there are many TLRs that recognize viral PAMPs, they signal through common adaptor molecules, including MyD88, MAL, TRAM, and TRIF. The TLR adaptor molecules signal through the IKKe/TBK1 complex and the IKKa/IKKb/IKKg complex similarly to RLRs, but can also recruit an IRAK-1/IRAK4/TRAF6 complex capable of activating the transcription factors IRF3, IRF7, and NF-kB. Activation of these transcription factors leads to the transcription of Type I IFNs and pro-inflammatory cytokines. Due to the considerable crosstalk between TLR and RLR signaling, it is difficult to discriminate between transcriptional products generated by the two sensor families, but it is likely that both play an important role in the innate immune response to SARS-CoV infection [68]

elevated. Importantly in ICU patients have a significantly higher level of GCSF, IP-10, MCP, and TNF- α; anti-inflammatory cytokines like IL-10 4 were also increased [47,57], IL-6 is a major driver in pathology and found to be in the highest level in non-survivors and critical patients (Figs. 5,6). The other pathways in severe COVID-19 where SARS CoV trigger the production of oxidized phospholipids that leads to IL-6 production by TLR4 through NFkB and MAPK signaling pathways N-Proteins of SARS-CoV-2 also induce IL-6 expressions [47]. Such a pro-inflammatory signature indicates a systemic exaggerated, pathological Innate Immunity response [27].

RIG-I like receptor signaling

The RIG-I Like Receptors are cytoplasmic sensors that detect viral RNA PAMPs in a wide range of cell types (Fig. 2). The RLRs RIG-I and MDA5 are ISGs that are transcribed during SARS-CoV infection *in vitro* [23]. MHV, another coronavirus, is recognized by MDA5 in brain macrophages and microglial cells, and by RIG-I and MDA5 in oligodendrocyte cells [44,45]. Although it is not known whether SARS-CoV is recognized by RLRs, MHV and SARS-CoV are likely to have similar replication intermediates (putative RLR ligands), so it is likely that SARS-CoV could be detected by the same sensors. RLR signaling leads to the activation of several transcription factors: IRF3, IRF7, and NF-kB. IRF3and IRF7 initiate transcription of Type I IFNs (IFN-a and IFN-b), important for an antiviral response. NF-kB mediated transcription of pro-inflammatory cytokines has been linked to the pathogenesis of ARDS [46]. *In vitro* SARS-CoVinfections have demonstrated that the expression of NF-kB generated transcripts, such as IL-6 and IL-8, happens as early as 12 h post infection, while IRF3/IRF7 transcription of Type I IFNs is delayed until 48 h post infection [23]. Similarly, in the macaque model of age-dependent SARS-CoV pathogenesis NFkB induced genes is more highly expressed in aged macaques that have significantly increased lung injury compared to young adult macaques where higher expression of IFNs was observed [40]. While the correlation of severe SARS-CoV disease with different transcriptional regimes is promising, the key to finding determinants of increased SARS-CoV pathogenesis may be how innate immune sensing mechanisms initiate transcription at critical junctures during infection and which types of innate immune sensing are protective.

SARS-COV2'S STRATEGIES TO EVADE INNATE IMMUNITY

Coronavirus has several strategies to evade innate immunity, including the evolution of low genomic CpG, RNA shielding, masking of potential key antigenic epitopes, and also inhibition of steps in IFN type I/III pathways [63].

Evading zinc-finger antiviral protein (ZAP) action

In mammals, the ZAP is also known as ZC3HAV1 and in humans, GAAP. It is an important part of the mammalian interferon-mediated immune response that binds to CpG dinucleotides in viral RNA genomes. It prevents viral replication and aids in the breakdown of viral genomes. SARS-Cov2 has the most severe cytosine-phosphate-guanosine (CpG) deficit of any beta coronavirus; hence, it is immune to ZAP [64].

RNA capping

The process of 5' end capping protects mRNA utilized by the host and viruses by limiting degradation and, more crucially, blocking recognition by cytosolic PRRs. SARS-CoV-2 has its own copping machinery, which consists of nsp10, nsp13, and the enzyme nsp16, which results in RNA caps that are indistinguishable from cellular mRNA caps. This helps to avoid detection by MDA5, IFIT, a protein that degrades target RNA [65].

PRR evasion by limiting its activity

Coronavirus works to evade the immune system by reducing PRR activity. The virus replicates in a double-membrane structure from the endoplasmic reticulum, which lacks PRRs, protecting it from both cytosolic and endosomal PRRs. The PRR signaling pathway is likewise suppressed. RIG is degraded by N-proteins, and coronaviruses decrease TLR signaling and cause TLR-associated signaling dysregulation [47].

TLR

In severe COVID 19 individuals, the SARS-CoV2 prevent successful immune response by inhibiting TRAF-3 and 6, has an essential role in inducing IRF-3/7 in response to activated TLR-7 [37].

To protect viral RNA and protein epitopes

SARS-Cov2 uses glycans and other post-translational modifications to mask immunogenic viral proteins epitopes during syncytia formation, allowing for the protection of viral RNAs, a protein generated during replication, in the use of replicase-transcriptase complex or replication organelle formed of double-membrane: Coronavirus uses glycans and other post-translational modifications to mask immunogenic viral proteins [63].

Inhibition in IFN production

SARS-Cov2 also developed techniques to block phases in the type I/III IFN production pathway. IFN antagonism has been attributed to a number of structural, non-structural, and accessory POTUS that interfere with the STING-TRAF3-TBK1 complex, preventing STING/TBK/IIKKE-induced type-I IFN production; signal transducer, and transcription activation, IRF3 NFkB signaling, as well as interfering with the action of ISG products such as IFTs [63]. Tetherin, also known as Bone Marrow Antigen 2), is inhibited by ORF7a [66].

CONCLUSION

The innate immune system's detection of distinct CoVs, as well as the inflammatory cell death pathways activated in response to diverse CoV infections, have been highlighted. For host defense, optimal cell death and inflammatory cytokine release are critical. However, in CoV-infected patients, excessive host inflammatory responses and cell death can result in cytokine storms and/or tissue damage, increasing morbidity and mortality. To decrease excessive inflammation while maintaining antiviral effects, CoV-induced innate immunity and cell death must be delicately managed.

When developing evidence-based treatment methods, it will be critical to mechanistically characterize the innate immune response to distinct CoV infections and evaluate the clinical efficacy of targeting innate immune pathways. SARS-CoV-2 infection, for example, suppresses type I and type III IFN production while increasing the expression of chemokines and pro-inflammatory cytokines [10], both of which are linked to a poor prognosis. Reduced innate antiviral defenses, as well as increased inflammatory cytokine production, could be some of the driving factors in CoV-mediated illnesses.

The SARS-CoV-2 epidemic is still spreading over the world, and we urgently need efficient treatments and vaccinations to tackle COVID-19. Given the urgency of the global health situation, researchers are looking into repurposing existing therapeutic agents that have been approved or are in development/testing for other infections, such as malaria (Plasmodium sp.), HIV, or other CoVs, or for blocking the inflammasome (e.g., colchicine) or the pro-inflammatory cytokines IL-1 and IL-6. The results of these treatments have been varied.

For example, despite having several comorbidities, all five patients in a recent pilot study of COVID-19 who were previously receiving colchicine treatment presented with mild/moderate illness and survived. However, because this was a tiny observational study, definitive results could not be drawn. Despite positive early evidence from retrospective and single-center investigations utilizing IL-6–antibody blockade therapy, current research have revealed that blocking IL-6 is linked to an increase in secondary infections, and big phase III trials using these inhibitors have yielded mixed outcomes [68]. A better knowledge of the mechanisms through which the innate immune system recognizes and responds to foreign substances will be key aspects for the development of putative therapeutic strategies.

AUTHOR'S CONTRIBUTION

Data collection, analysis and writing – Dr Murugan N; Data collection and writing – Ms. Arulmozhi; Data analysis, manuscript correction, and rewriting – Dr Chirayu P.

CONFLICTS OF INTERESTS

The authors have no conflict of interests.

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