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Review Article

Severe Acute Respiratory Syndrome Coronavirus 2 Dynamics of Human Infection: Molecular Biology, Virology, and Immunology

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Abstract

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has become a global public health menace because of its immunopathogenesis and faster transmission than prior coronaviruses that infected people. Due to the genetic similarity between SARS-CoV and MERS-CoV infections, knowledge from earlier SARS-CoV and MERS-CoV infections has been used to infer the mechanism behind the host immune response during the infection with SARS-CoV-2 even though this knowledge is incomplete. The hyperactivation of macrophages and monocytes, which results in autophagic cell death and increases interleukin-6 and neutrophil levels, is evidence for this. It has been proposed that SARS-CoV-2 undermines the host's immune system by blocking interferon induction and signaling, which contributes to a cytokine storm that may result in acute respiratory distress syndrome and multiple organ failure while reducing the host's adaptive immunological responses. This work gives a broad review of the molecular dynamics of SARS-CoV-2 infection from the viewpoints of molecular biology, virology, and immunology in order to clarify and critically characterize the immunopathogenesis of SARS-CoV-2 and how it can alter sickness severity. Thus, this would enlighten us on potential new therapeutic avenues for future studies.

Introduction

Coronaviruses (CoVs) are a large family of pathogenic viral microorganism that infect people and a wide range of animal species, thus causing diseases ranging in severity in the respiratory, gastrointestinal, hepatic, and neurological systems. There are four positive-sense RNA viruses of CoVs, and these have been designated alpha, beta, gamma, and delta.[1,2] Gammacoronaviruses and Deltacoronaviruses primarily infect birds, while the Alphacoronavirus and Betacoronavirus typically infect people.[3] The past two decades have seen the emergence and spread of respiratory-related diseases, including the severe acute respiratory syndrome coronavirus (SARS-CoV), which was first identified in bats in 2003. The disease was considered to have propagated to an intermediate animal host, the civet cat, and other wild animals before making its impact on the human population in Guangdong Province, China in 2002.[4,5] Subsequently, the SARS-CoV epidemic spread rapidly throughout Eastern Asia and to 32 other countries causing 919 deaths in 8,422 infected individuals.[6] Interestingly, SARS-CoV showed an aggressive clinical outcome with advanced age (>60 years), and was rarely detected, or appeared to follow a less aggressive clinical course in young children.[7,8] Middle East Respiratory Syndrome (MERS-CoV) was first reported in Saudi Arabia in June 2012, and the infection was thought to have occurred directly or indirectly through contact with infected dromedary camels. Ac-

Keywords: SARS-CoV-2; Genome; Angiotensin converting enzyme 2; Cytokine storm; COVID-19.

Abbreviations: ACE2, angiotensin-converting enzyme 2; APC, antigen presenting cells; COVID-19, Coronavirus disease 2019; CoVs, coronaviruses; ER, endoplasmic reticulum; ERGIC, endoplasmic reticulum-golgi intermediate compartment; MERS-CoV, Middle East Respiratory Syndrome; RNA, ribonucleic acid; RTC, replication-transcription complex; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TMPRSS2, transmembrane serine protease 2.

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Table 1. Recent statistics on the emergence and widespread distribution of SARS-CoV-2 in the top 10 countries globally

Country	Total cases	Total recovered	Active cases	Total deaths
United States	96,716,573	92,706,128	2,937,150	1,073,295
India	44,472,241	43,893,590	50,594	528,057
France	34,623,098	34,121,748	347,017	154,333
Brazil	34,538,882	33,546,726	307,510	684,646
Germany	32,344,032	31,557,700	638,351	147,981
South Korea	23,791,961	22,102,194	1,662,518	27,249
United Kingdom	23,521,792	23,246,116	87,434	188,242
Italy	21,969,725	21,222,429	571,344	175,952
Russia	19,857,571	18,876,316	596,279	384,976
Japan	19,635,246	18,114,017	1,479,654	41,575

Last accessed date: September 07, 2022.

cording to the examination of various virus genomes, in contrast to many viruses which are zoonotic, the CoVs are a classical example of a spill over event with its origins believed to be bats.[9,10] Despite the fact that MERS-CoV was less efficiently transmitted to humans than SARS-CoV, it had a high mortality rate of approximately 37% of reported patients with a MERS-CoV infection.[11,12]

The age range 30–39 years had the highest risk of secondary infections from MERS-CoV infections, while fatality rates were greater in the age groups 50–59 years for the main cases and 70–79 years for secondary cases. Statistics have shown that there were 2,519 laboratory-confirmed cases of MERS-CoV reported worldwide with 866 deaths as of January 2020 with most cases from Saudi Arabia with 2,121 cases and 788 deaths.[13] Since the initial SARS-CoV outbreak 18 years ago, another ongoing novel coronavirus emerged in December 2019 designated SARS-CoV-2 that caused the Coronavirus disease 2019 (COVID-19). The outbreak of SARS-CoV-2 was thought to have started in a seafood wholesale market in Wuhan, Hubei Province, China.[14] Although there is currently no evidence linking SARS-CoV-2 to a specific wildlife host, a phylogenetic relationship with bat and pangolin coronaviruses has been suspected.[15–17] Recent molecular and phylogenetic analyses, however, have debunked the notion that pangolins could be a possible intermediate source of SARS-CoV-2 transmission to humans.[18,19]

SARS-CoV and SARS-CoV-2 may both cause disease via comparable pathways as a result of the present emerging virus being more similar to the former variant than MERS-CoV.[15,20,21] Patients over 60 years have larger clinical symptoms, greater severity, and longer disease courses than those under 60 years, thereby suggesting that SARS-CoV-2 clinical characteristics and prognosis resemble those of SARS-CoV and MERS-CoV.[22,23] According to the World Health Organization's statistics on SARS-CoV-2, as of September 7, 2022, there were 611,532,756 confirmed cases and 6,507,543 confirmed deaths globally with the United States of America having the highest number of reported cases (96,716,573) and deaths (1,073,295) (Table 1). During the same period, Africa recorded 12,041,842 confirmed cases and 255,560 confirmed deaths with South Africa having the highest number of reported cases (4,012,920) and deaths (102,108) (Table 2).[24–27]

Given the negative health impact of the COVID-19 pandemic based on the SARS-CoV-2 genome, appropriate therapeutic strategies and effective control practices would be necessary to curb the further spread of the pandemic. This review will therefore focus on the molecular biology, virology, and immunology aspects of SARS-CoV-2 as dynamics that would enable its infectivity and spreadability.

Table 2. Recent statistics on the emergence and widespread distribution of SARS-CoV-2 in the top 10 African countries

Country	Total cases	Total recovered	Active cases	Total deaths
South Africa	4,012,920	3,904,513	6,299	102,108
Morocco	1,264,580	1,248,016	290	16,274
Tunisia	1,144,824	N/A	N/A	29,238
Egypt	515,645	442,182	48,850	24,613
Libya	506,864	500,361	66	6,437
Ethiopia	493,278	471,675	14,031	7,572
Kenya	338,243	332,443	126	5,674
Zambia	333,124	328,787	320	4,017
Botswana	325,911	322,955	178	2,778
Algeria	270,476	322,955	81,490	6,879

Last accessed date: September 07, 2022.

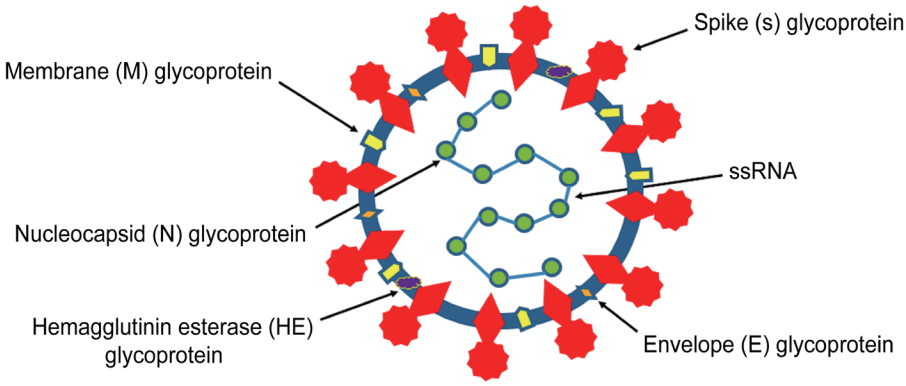

Fig. 1. General structure of SARS CoVs. The structure of SARS-CoV-2 showing the main structural glycoproteins.

Molecular biology of SARS-CoV-2

The genome of the CoVs functions as a messenger RNA for translating polyproteins with replicase activity to a 3′ poly (A) tail that is roughly 250–500 nts long and comes before the poly (A). Comparatively, accessory and structural proteins constitute 10% of the viral genome, while the replicase gene that encodes the non-structural proteins is thought to occupy about two-thirds (20 kb) of the genome.[28,29]

SARS-CoV-2 has a reported average length of 30,000 bases. The 5′UTR (–265 nucleotides) and 3′UTR (–358 nucleotides), two adjoining regions that are not translated, are present in the genome along with 14 ORFs that encode 27 proteins.[30] The four core structural proteins of SARS-CoV-2 are the spike (S) glycoprotein, envelope (E), membrane (M), and nucleocapsid (N), and the virus also possesses eight accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and orf14), which are located in the 3′terminus' of the genome. The S, E, and M proteins cooperate to produce the viral envelope (Fig. 1), while the N protein maintains the stability of the RNA genome.[31]

While the majority of auxiliary proteins are not required for viral replication, some have been shown to be important for virus pathogenesis.[28] Because of its location in the respiratory system, SARS-CoV-2 is more virulent than SARS-CoV and MERS-CoV, which are thought to replicate in the lower respiratory tract extremities according to a review by Sariol *et al*.[32] Additionally, SARS-CoV-2, purportedly differs from SARS-CoV at the level of the basic protein building units, which could affect the pathophysiology and functionality of the virus. The 8b protein is longer (121 amino acids) than the 8a protein (84 amino acids) although the 3b protein is shorter; for example, SARS-CoV-2 lacks the 8a protein that is present in SARS-CoV.

Spike (S) glycoprotein

The S-protein, which is generally 180 kDa in size, contains both the receptor binding N-terminal S1 domain, and the cell membrane fusion C-terminal S2 domain.[33] S-protein is heavily N-glycosylated and tactically through cleavage of signal peptide tethered to the amino terminal domain that enters the endoplasmic reticulum (ER). The S-amino protein has a wide ectodomain, an anchor that traverses transmembrane once, and an intracellular short tail at its C-terminus. The spike structure on the virus surface is created by the trimers of the S-protein. The interface between the S1 and S2 subunits of CoVs, which are still covalently bound to one another in the prefusion conformation, is where the S-protein is normally disrupted.[34,35] The S1 subunit with the receptor-binding activity makes up the top of the S trimer and steadies the S2 fusion machinery, a viral membrane anchor. A furin-like protease frequently cleaves the S-protein activating it for membrane fusion by resulting in significant, irreversible conformational changes.[36,37] The S-protein thus becomes crucial for cell adhesion and entry into host cells with the aid of transmembrane serine protease 2 (TMPRSS2) and a spike protein receptor binding domain (RBD) that specifically binds to the angiotensin-converting enzyme 2 (ACE2) present in the host membrane.[38,39]

Envelope (E) glycoprotein

The E-protein is a small, 8.4–12 kDa integral membrane protein that is present in all coronaviruses.[40,41] It has three domains: a C terminus, a long hydrophobic transmembrane domain, and a short hydrophilic amino terminal domain.[42] It is primarily found in the endoplasmic reticulum and the Golgi complex, where it plays a role in the CoV assembly, budding, ion channel activity, and intracellular trafficking of infectious virions.[43–45] Despite being a minor part of the virus, it is abundantly expressed and found inside infected cells.[43–45] Although SARS-CoV does not appear to require the protein for replication, abrogation of the gene producing the E-protein causes a gradual amplification of the virus.[46] SARS-CoV-2 E-protein sequence analysis has revealed that it differs from other SARS-CoV-2 E-variants in a number of ways but shares sequences with pangolins (CoV MP798) and bats (CoV CoVZXC21, CoV-ZC45, and RaTG13 isolates). The SARS-CoV-2 E-protein shares the same amino acid profile as SARS-CoV with no changes.[30,40,47]

Membrane (M) glycoprotein

With three transmembrane domains that give the virion its form and size, the M-protein is the most prevalent structural protein that maintains the viral envelope.[42,48] It is a 25–30 kDa protein with a variety of amino acid sequences in different coronaviruses that is structurally comparable and conserved across coronaviruses.[48,49] The M protein has a long C-terminal endodomain that is co-translationally inserted into the endoplasmic reticulum membrane and a short, glycosylated ectodomain at the N-terminus. The protein, which is present in the virion as a dimer, helps to bend the membrane and binds to the nucleocapsid.[50]

Nucleocapsid (N) protein

The only structural protein connected to the nucleocapsid is the N-protein, which has a molecular weight between 43–50 kDa.[51,52] It has two RNA substrates, the genomic packing signal and the transcriptional regulatory sequence, and is made up of three domains: an RNA-binding domain, an N-terminal domain,

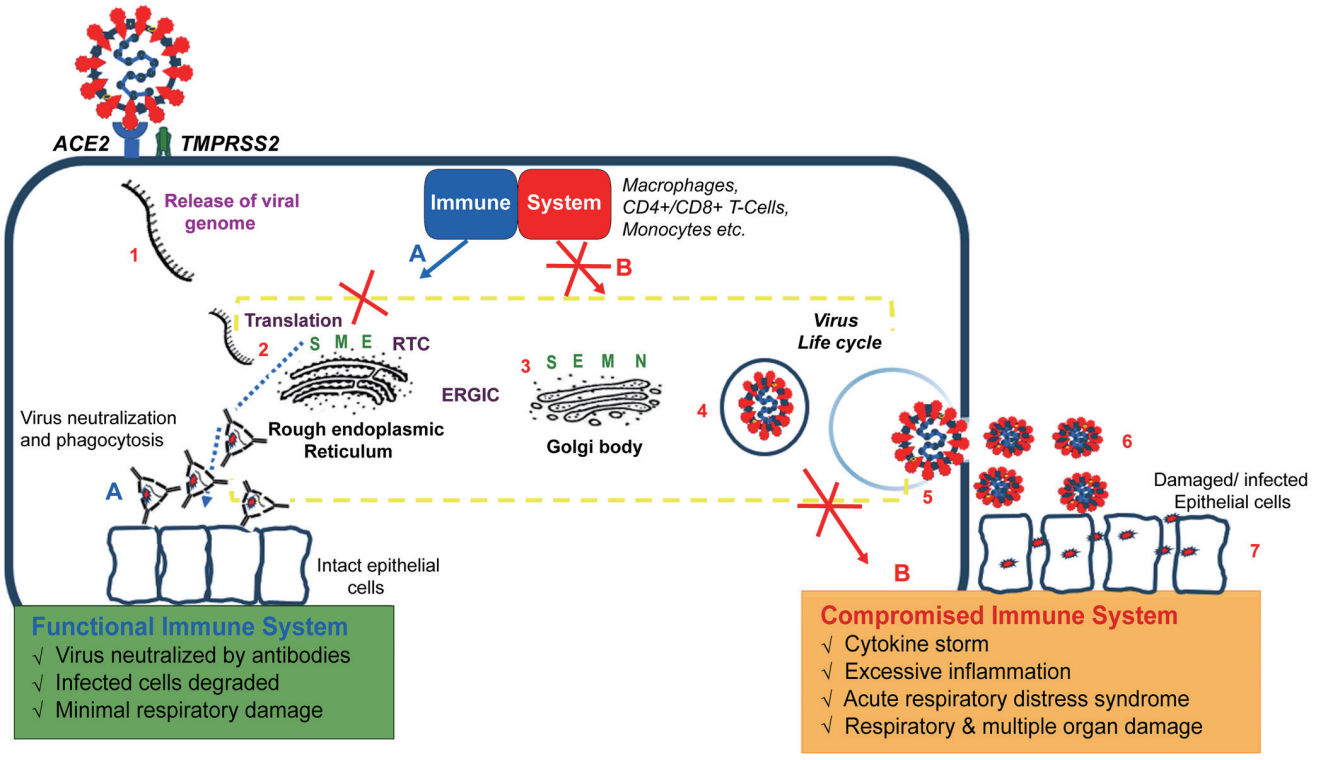

Fig. 2. Life cycle and host immune response to SARS-CoVs. Following the attachment of SARS-CoV-2 to the host cell with the aid of ACE2 and TMPRSS2. (1) Viral genome released; (2) translation takes place with the aid of RTC, and the membrane-bound structural proteins, M, S, and E, are inserted into the R.ER, (3) virus assembly and packaging takes place at the ERGIC, (4) the virus is transported in the smooth walled vesicle; (5) virus releases exocytosis, (6) virus is ready to infect other host cells, (7) other host cells are infected, and the life cycle begins again. (A) Immune system via the APC neutralizes/phagocytizes the virus and eliminates the infected cells. (B) Dysfunctional immune system enables the assembly and transport of the newly synthesized virions to infect other host cells. ACE2, angiotensin-converting enzyme 2; APC, antigen-presenting cells; E, envelope; ERGIC, endoplasmic reticulum-Golgi intermediate compartment; M, membrane; R.ER, rough endoplasmic reticulum; RTC, replication-transcription complex; S, spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TMPRSS2, transmembrane serine protease 2.

and a C-terminal domain.[53–55]

The viral replication cycle, the viral genome, and the host cell's biological response to viral infections are all activities that are influenced by each N-protein domain's ability to bind to RNA.4.[2,56–58] Additionally, it is heavily phosphorylated, which may allow for structural alterations that would boost its affinity for viral RNA.[59] Moreover, the N-protein interacts with the M-protein and non-structural protein 3 to help pack the viral genome into viral particles.[56,60,61]

Hemagglutinin-esterase protein

A subset of Betacoronaviruses includes a short structural protein called hemagglutinin-esterase, which functions as a hemagglutinin to bind the sialic acids of the surface glycoproteins. The facilitation of S-protein-mediated cell entry and viral dissemination across the mucosa is assumed to be caused by this binding to sialic acid and the esterase activity.[62,63]

Viral entry into the host cell

The S-protein and its cognate receptor interplay cause the CoV attachment and entry into the host cell. Type II pneumocytes and bronchial epithelial cells are respectively infected by SARS-CoV and MERS-CoV using the ACE2 and Dipeptidyl peptidase-4/CD26 receptors.[64,65] Shang *et al*. identified minor but functional differences between SARS-CoV and SARS-CoV-2 in receptor recognition that allowed SARS-CoV-2 RBD to have a substantially higher ACE2 binding affinity than SARS-CoV RBD and sustain competent cell penetration, while avoiding surveillance brought on by the immune system (Fig. 2).[66] In addition to the respiratory tract (including the lungs associated type II alveolar cells, and nasal epithelial cells, particularly goblet/secretory cells and ciliated cells), the stratified epithelial cells in the upper esophagus, myocardial cells, adipose tissue, and absorptive enterocytes from the ileum and cholangiocytes have been shown to massively express the ACE2 receptors.[67–69] Patients infected with SARS-CoV-2 consequently experience problems with their kidneys, heart, muscles, and digestive system.[70,71]

Men are more susceptible to SARS-CoV-2 infection than women because they express ACE2 at higher levels compared to women.[72,73] Men had greater plasma concentrations of ACE2 than women, according to Sama *et al*'s analysis of two independent cohorts of heart failure patients, which explained why men had a higher incidence and mortality rate for COVID-19.[74] However, SARS-CoV-2 has only sometimes been seen in fetuses or infants of SARS-CoV-2-infected mothers, and it is improbable that this would infect the human placenta according to Pique-Regi *et al*. According to the study, the receptor and enzyme TMPRSS2 and ACE2, respectively present in an extremely minute concentration, which are required for viral entrance into the host cell, were not

produced by the placental membranes.[75]

SARS-CoV-2 could enter the body in two different ways: either by plasma membrane fusion or through endosomes. The S-protein and the host receptor ACE2 controlled the entry in both cases.[35,38] Furin also had additive effects with lysosomal cathepsins and TMPRSS2 on activating SARS-CoV-2 binding and entry.[38,76,77] When SARS-CoV-2 entered, it released genomic material in the cytoplasm that was prepared for protein translation. Polyprotein 1a/pp1ab transcription is started by the replication-transcription complex (RTC).

The main protease, or protease which was like chymotrypsin was involved in minus-strand RNA synthesis, genome replication, and subgenomic RNA, cleaved these pp1a and pp1ab's nsps 1–11 and 1–16, respectively, into individual nsps.[78,79] Each of these nsps had a specific role in the CoV replicative structures where viral RNA production occurred.[29,80–83] The smaller RNA molecules (subgenomic RNA) then produced the M, S, and E proteins, which were expressed at the protein level and interleaved into the ER, where they travelled into the endoplasmic reticulum-golgi intermediate compartment (ERGIC) via a secretory pathway, where mature virions were formed.[84,85]

The majority of protein-protein interactions were directed by the M protein, whereas the E protein caused membrane curvature, and the N protein promoted the production of virus-like particles inside the ERGIC.[86,87] Despite being integrated into the virions at this stage, the S-protein was not necessary for assembly. The link between the S-protein and M-protein was essential for its inclusion into the virions, as the M-protein also attached itself to the nucleocapsid and promoted the completion of the virion assembly.[88]

The structural and accessory proteins also contributed to the pathogenicity of SARS-CoV-2 by suppressing the innate immune response, thus enabling the assembly and transport of freshly synthesized virions to the cell's surface in smooth walled vesicles and exporting them out of the cell via exocytosis in search of another host cell to infect.[29,89]

Host immune responses

In most cases, when a virus enters a host cell, antigen-presenting cells (APC) initially activate the host's innate immune system. Due to the genetic similarity between the SARS-CoV and MERS-CoV infections, the mechanism underlying the host immune response during SARS-CoV-2 infection was not thoroughly investigated.[15,90] As with SARS-CoV, the host immune system's early reaction to SARS-CoV-2 was primarily mediated by cytokines targeting pneumocytes I and II and alveolar macrophages.[90,91] Following SARS-CoV-2 infection, the macrophages and monocytes became hyperactive, which increased the IL-6 production, neutrophil production, and lymphocytopenia by causing T-cell death.[91–93] Major histocompatibility complex I presented the viral antigenic peptides to the CD4+ T-helper cells once they entered the tissue cells. This caused the release of IL-12, which further promoted Th1 cell activation. Numerous pro-inflammatory cytokines and chemokines were produced via the NF-kB signaling pathway, and these molecules attracted the neutrophils and monocytes to the site of SARS-CoV-2 infection.[94]

After Th1 cell activation, CD8+ cytotoxic T cells may be stimulated, which would cause them to hunt for and kill virus-infected cells.[95–97] IgM and IgG antibodies were also typically produced after SARS-CoV-2 infection; the IgM antibody response was specific and visible during the first week, but the IgG antibody response was long-lasting and typically results in lifetime immunity.[96,98,99] Furthermore, SARS-CoV-2 mortality has been linked to low numbers of CD4+ and CD8+ T lymphocytes.[100,101]

In addition, the release of numerous chemokines and cytokines, including CCL2, CCL3, IL-2, IL-6, IL-7, IL-10, IL-12, IL-18, G-CSF, MCP-1, MIP-1, TGF-beta, TNF, CXCL-10, CCL-5, etc., has been observed in previous SARS-CoV and MERS-CoV pandemics.[102–104] As documented in the case of SARS-CoV-2,[105–107] this large release of cytokines (cytokine storm) could then cause acute respiratory distress syndrome, respiratory failure, and multiple organ failure that would ultimately result in death.

Immune evasion

Like most viruses, CoVs have developed diverse immune evasion tactics of surviving and infecting host cells.[96,108] Due to the paucity of particular information on how SARS-CoV-2 avoids immune detection and inhibits human immune responses, studies on SARS-CoV and MERS-CoV have been used to draw conclusions.[109]

It has thus been hypothesized that the development of double-walled vesicles on the cell's surface protects viral pathogen associated molecular patterns from being recognized by cytosolic pattern recognition receptors.[96] SARS-CoV-2 has been able to maintain effective cell entry, while eluding immune monitoring because of the RBD's strong ACE2 binding affinity and furin preactivation of the S-protein.[66,77] Once inside the host cell, nsps could help CoVs avoid the immune system; for example, nsp1 could decrease the activity of IFN-I causing the disease to become more severe.[110,111] The inhibition of interferon induction and signaling by SARS-CoV-2 has been suggested to lead to the high activation of pro-inflammatory cytokines and macrophages thus impairing the host adaptive immune responses.[107,112,113]

Future Direction

SARS-CoV-2 infection is believed to have a complicated process that involves immune reactions against infected cells and in viral replication. As a result, in order to develop new treatment strategies for COVID-19, the mechanisms underlying immunological abnormalities and viral replication in COVID-19 patients must be identified. Therefore, future research should concentrate on comprehending the cellular process behind the immunopathogenesis of SARS-CoV-2 and how it could influence the severity of the disease.

Conclusions

This review has described the SARS- CoV-2's molecular dynamics and the ways in which the virus uses its structural and auxiliary proteins to outwit the host's defense system and cause death. In addition to its structural capabilities, SARS-CoV-2 exhibits an unanticipatedly high rate of worldwide transmission and spread, which is brought on by travel, a lack of timely public health interventions, and asymptomatic viral carriers. To develop novel therapy options specifically aimed at reducing the impact of COVID-19, it is crucial that investigations concentrate on understanding the immunopathogenesis of SARS-CoV-2 and how it could contribute to disease severity.

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Conflict of interest

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Author contributions

Conceived and designed the review: LM. Write-up: LM, JA, HO, JK, and MZ. All authors approved the final version of the manuscript.

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