Current Topics in Virology
Vol. 18, 2021

Review

SARS-CoV-2 morphology, genome, life cycle and our bodies' immune response: a review

Ilyes Zatla*, Lamia Boublenza and Hafida Hassaine

Laboratory of Microbiology Applied to the Food Industry, Biomedical and the Environment, Faculty of Nature and Life Sciences, Earth and Universe Sciences, University of Tlemcen, Algeria.

ABSTRACT

A novel coronavirus strain has been testing the capabilities of our modern world and suffocating health care systems, while bringing together scientist's researches and governmental powers, to fight off its robust viral disease. A new zoonotic pathogenic member of the human coronaviruses, that was first documented in Wuhan, China, has crossed the species barrier to infect humans and caused an outbreak of viral pneumonia. In this brief review, we'll discuss the virology of SARS-CoV-2, the virus that causes COVID-19, covering the general structure of the virus, its genetics and its process of replication. SARS-CoV-2 gets into the cell through the recognition of the angiotensin-converting enzyme 2 (ACE2) receptors by the spike glycoprotein, with the aid of the priming protein transmembrane serine protease 2 (TMPRSS2), which is important for its activation, and replicates as a result of a complex process that involves RNA synthesis, proofreading and capping.

KEYWORDS: SARS-CoV-2, COVID-19, replication, ACE2, pandemic, pneumonia.

1. Introduction

About 70% of the emerging pathogens infecting humans originate from animals, and coronaviruses (CoVs) make the forefronts of these pathogens [1]. Among the viral-mediated pandemics that have been rapidly spreading worldwide in the last twenty years, CoV-dependent outbreaks seem to be the most severe, with involvements in pulmonary pathology [2]. Therefore, the increasing frequency of the emergence of zoonotics that have crossed species barrier to infect humans, resulting in respiratory illnesses including a pneumonia that is fatal [3], is of grave concern because of their high mortality rate [4]. Moreover, new coronaviruses appear to emerge periodically in humans, mainly due to the high prevalence and wide distribution of coronaviruses, the large genetic diversity and frequent recombination of their genomes, and the increase of human-animal interface activities as well [5].

SARS-CoV-2 is the seventh pathogenic member of the human coronaviruses [6], a new zoonotic virus [7], that has crossed the species barrier to infect humans [8], and evolving rapidly where aged mutations are persisting or diluted away and new mutations are arising [9], causing severe respiratory syndrome in humans [10].

The virus is highly contagious, spreading quickly around the world, affecting all individuals, especially the elderly, and those with diverse genetic and immunological backgrounds, notably those with multiple underlying disorders from countries with varied demographics and environmental conditions [11].

The severity of the disease is most often an important indirect factor in the ability of the virus to spread [8]. Complications are mainly associated with virus load, virulence, route of infection, age and immune status of the host [11].

*Corresponding author: ilyes.zatla@aol.com

2. Structure

The virion is spherical, approximately 120 nm in diameter with a helical nucleocapsid enveloped by a host-derived lipid bilayer, that possesses crown-like distinctive spikes, about 9 to 12 nm, on their surface with an RNA genome packaged into it [12] (Figure 1).

3. Genome

SARS-CoV-2 has a non-segmented, positive-sense, single-stranded RNA (+ss RNA), containing a 30 kb genome with 14 open reading frames (ORFs) and 38% G+C content, encoding 9,860 amino acids (AA), representing the viruses with the largest known RNA genomes [13]. The genome encodes for both structural and non-structural proteins (Nsp) with different functions [12-14] (Figure 2).

The genomic RNA has a 5’ cap and a poly-A 3’ tail with genome characterization showing two flanking untranslated regions, the 5’UTR -265 nucleotides and the 3’UTR -358 nucleotides-long [13, 15].

Structural proteins encoded by the 3’-terminus include spike glycoprotein (S; consists of 2 domains—S1 and S2), envelope protein (E), membrane protein (M), and nucleocapsid protein (N) [12, 14], and the 5’-terminal of the genome consists of accessory genes that are species-specific and encode polyproteins pp1a and pp1b, where pp1a is further divided into nonstructural proteins (Nsps) that participate in genome transcription and replication [13].

ORF1ab is a large polyprotein encoding sixteen non-structural proteins: nsp1 (suppresses the antiviral host response), nsp2, nsp3 (a papain-like protease), nsp4, nsp5 (3C-like proteinase), nsp6, nsp7 and nsp8, making a complex to form a primase, nsp9 (responsible for RNA/DNA binding activity), nsp10, nsp12 (RNA-dependent RNA polymerase) (RdRp), nsp13 (helicase), nsp14 (3’- to 5’ exonuclease), nsp15 (endoribonuclease), and nsp11 [9, 15, 16]. In particular, ORF1ab gene which encodes replicase/transcriptase, which is required for viral genome replication, with the incorporation of a polybasic cleavage site in the viral RNA, may be important for viral pathogenesis and transmissibility [12, 17].

4. Life cycle of the virus

Human coronaviruses utilize host cellular components to achieve various physiological processes, including viral entry, genomic replication,

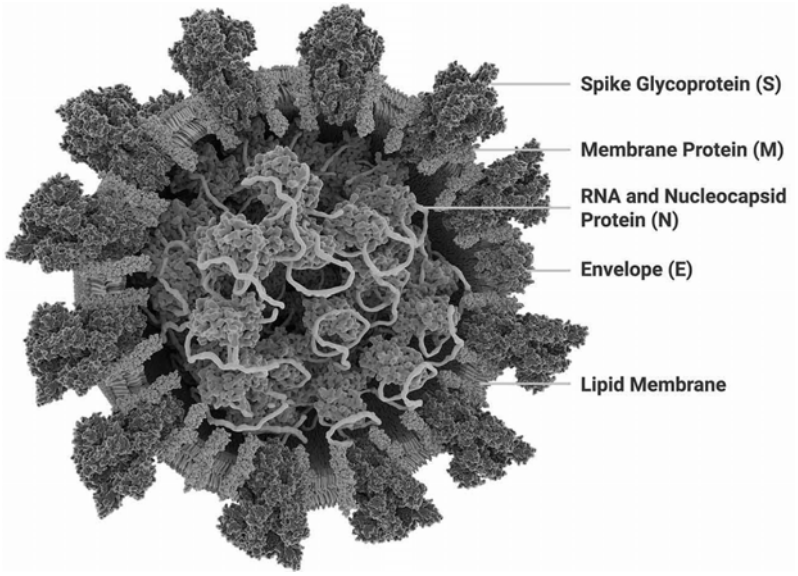

Figure 1. Structure of SARS-CoV-2. © 2022 Promega Corporation. Reproduced with permission from Promega Corporation.

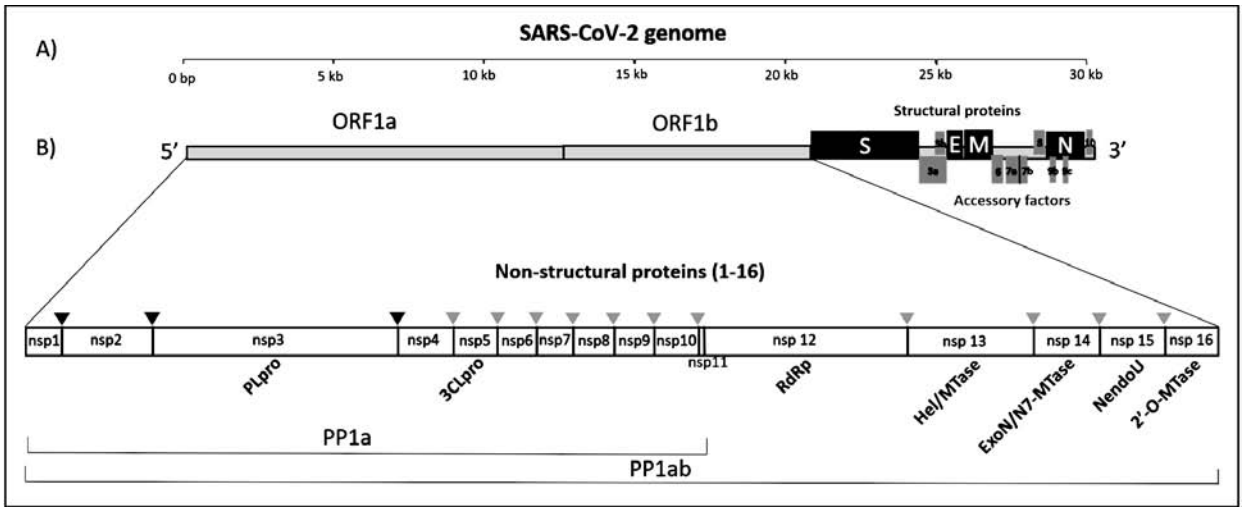

Figure 2. Schematic diagram of SARS-CoV-2 polycistronic genome (A); genome of SARS-COV-2 organized in individual ORFs (black/grey triangles = cleavage sites) (B). Reproduced with permission from Romano, M.; Ruggiero, A.; Squeglia, F.; Maga, G.; Berisio, R. A. Structural View of SARS-CoV-2 RNA Replication Machinery: RNA Synthesis, Proofreading and Final Capping. *Cells* 2020, *9*, 1267 [15].

the assembly and budding of virions, thereby resulting in pathological damage to the host [18]. It is widely accepted that coronavirus human transmissibility and pathogenesis mainly depend on the interactions, including virus attachment, receptor recognition, protease cleaving and membrane fusion, of its transmembrane spike glycoprotein (S-protein) receptor-binding domain, specific cell receptors, and host cellular trans-membrane serine protease [19]. SARS-CoV-2 replication has a complex process which involves RNA synthesis, proofreading and capping [15].

4.1. Viral entry

All CoVs encode a surface glycoprotein, a spike anchored in the viral envelope which binds to the host-cell receptor and mediates viral entry, since cell entry is an essential action for cross-species transmission [20]. CoVs' S proteins (S) are (~1200 aa long) typical class I viral fusion proteins, that contributes to the recognition and binding to the cell receptor, tissue tropism and pathogenesis [1, 21]. They consist of three domains: an extracellular domain (EC), a transmembrane anchor domain and a short intra-cellular tail. EC has two functional subunits, a receptor-binding subunit S1 (it contains two independent domains, an N-terminal domain (S1-NTD) and a receptor binding domain (RBD), which plays a key role in receptor recognition and binding and a membrane-fusion subunit S2 (C-terminal S2-membrane-anchored protein at the S2' site), with a protease cleavage required for activation of the fusion potential, of the S protein [15, 20, 22, 23, 24].

Receptor recognition by coronaviruses is an important determinant of viral infectivity, tissue tropism, pathogenesis and host range [21, 22]. SARS-CoV-2 gets into the cell through the recognition of the Angiotensin Converting Enzyme 2 (ACE2) receptors by the spike glycoprotein [15, 25, 26]. These receptors belong to the ACE family that consists of an N-terminal peptidase domain (PD) and a C-terminal collectrin-like domain (CLD) [27]. Angiotensin-converting enzyme (ACE) and its close homologue ACE2, while both belonging to the ACE family of dipeptidyl carboxydipeptidases, serve two opposing physiological functions. ACE cleaves angiotensin I to generate angiotensin II, the peptide which binds to and activates AT1R to constrict blood vessels, thereby elevating blood pressure; on the contrary ACE2, inactivates angiotensin II while generating angiotensin, a heptapeptide having a potent vasodilator function *via* activation of its Mas receptor [28]. Although ACE2 is hijacked by some coronaviruses, its primary physiological

role is in the maturation of angiotensin (Ang), a peptide hormone that controls vasoconstriction and blood pressure. [27]. ACE2 is essentially a carboxypeptidase, which can remove carboxy-terminal of hydrophobic or basic amino acids [29]. Full-length ACE2 consists of an N-terminal PD and a C-terminal collectrin-like domain (CLD) that ends with a single transmembrane helix and a ~40-residue intracellular segment; the PD of ACE2 cleaves Ang I to produce Ang-(1-9), which is then processed by other enzymes to become Ang-(1-7). ACE2 can also directly process Ang II to give Ang-(1-7) [27].

SARS-CoV-2 seems to have an RBD that binds with high affinity to ACE2 from humans, ferrets, cats and other species with high receptor homology [6]. Its RBD has a twisted five-stranded antiparallel β sheet (β1, β2, β3, β4 and β7) with short connecting helices and loops that form the core with an extended insertion called the RBM, which contains most of the contacting residues of SARS-CoV-2 that bind to ACE2 [24]. The RBM is a region in the carboxy-terminal half of the RBD that contains all of the residues that interface with the host receptor [20]. SARS-CoV-2 S-protein-RBD and ACE2-PD interactions have identified important key residues. The S-protein ectodomain RBD was reported to bind to ACE2-PD with ~10- to 20-fold higher affinity (~15 nM) when compared to the SARS-CoV S-protein-RBD, potentially contributing to high rate of SARS-CoV-2 infection [3, 6, 27].

Structural and computational analyses predict that SARS-CoV-2 not only uses human ACE2 as its host receptor, but uses it more efficiently, and show that the RBD-ACE2 interaction is not ideal but it is more optimized [20, 30, 31, 32]. Thus, the high-affinity binding of the SARS-CoV-2 spike protein to human ACE2 receptor is most likely the result of natural selection on a human or human-like ACE2 receptor that permits another optimal binding solution to arise [30]. Enhanced binding affinity between SARS-CoV S and hACE2 was proposed to correlate with increased virus transmissibility and disease severity in humans [21]. The binding affinity alone is unlikely to explain the unusual transmissibility of SARS-CoV-2, since, the unique '-RRAR-' furin cleavage site (FCS) at the S1–S2 boundary of the SARS-CoV-2 spike protein, was found to have a role in facilitating the rapid human-to-human transmission [6, 22, 24]. However, a recent study showed that FCS may not be as critical for the high binding capacity of the virus, as previously believed [28].

Transmembrane serine protease 2 (TMPRSS2) priming is important for SARS-CoV-2 S protein activation [1]. It cleavages the C-terminal segment of ACE2 and enhances the S protein–driven viral entry [23, 27]. ACE2 and TMPRSS especially TMPRSS2 are co-localized in the same host cells, the latter exerts hydrolytic effects responsible for S-protein priming and viral entry into target cells [19, 23]. But TMPRSS2 was only expressed in a subset of ACE2+ cells, suggesting that the virus might use alternative pathways, especially cathepsin B, which was expressed in more than 70-90% of ACE2+/TMPRSS2- cells [25].

Yet another human receptor, CD147 (also known as Basigin or extracellular matrix metalloproteinase inducer (EMMPRIN)), has recently been identified as a possible route of viral entrance [12, 15].

Gene ontology enrichment analysis showed that the ACE2-expressing AECII genes have high levels of multiple viral process-related genes, including regulatory genes for viral processes, viral life cycle, viral assembly, and viral genome replication suggesting that the ACE2-expressing AECII facilitates coronaviral replication in the lung [33], and TMPRSS2 is a host cell factor that is critical for the spread of several clinically relevant viruses, including coronaviruses [23].

4.2. Replication

The replication of the virus begins after the binding of its spike protein (S) on the cell surface of ACE2 molecules of the host [18, 33]. The trimetric S-protein is processed at the S1/S2 cleavage site by TMPRSS2 into an N-terminal S1-ectodomain that recognizes the ACE2 cell surface receptor which facilitates viral attachment, and a C-terminal S2-membrane-anchored protein at the S2 site and allows fusion of viral and cellular membranes involved in viral entry [15, 23], A successful host cell invasion by the virus involves direct binding of the virus S1 receptor binding domain (RBD) to the host ACE2 peptidase

extracellular domain (PD), exposing the S1-S2 inter-domain protease site that upon cleavage by host proteases leads to S2-mediated virus-host cell membrane fusion [3]. Primary viral replication is presumed to occur in mucosal epithelium of upper respiratory tract (nasal cavity and pharynx), with further multiplication in lower respiratory tract and gastrointestinal mucosa [34]. Once inside the cell, the infecting RNA acts as a messenger RNA (mRNA), then will be translated by host ribosomes to produce the viral replicative enzymes, in which the viral RdRp generates new RNA genomes and the mRNAs for the synthesis of the components necessary to assemble the new viral particles inside the cytoplasm of the cell [15, 35].

ACE2 is expressed on many cells resulting in a profound immune response and widespread endothelial dysfunction [36]. It is abundantly expressed in the lungs including airways, cornea, esophagus, ileum, testis respiratory tree, the heart, the glandular cells of gastric, duodenal, and rectal epithelia, kidney, liver, gallbladder, common bile duct and intestinal tissue, supporting the entry of SARS-CoV-2 into the host cells [25, 27, 32, 33]. Low viral RNA was also detected in esophageal mucous tissue [32], with a possibility of salivary gland infection [19, 31], but SARS-CoV-2 mainly invades the mouth and alveolar epithelial cells type-I and type-II, resulting in respiratory symptoms [29, 25]. ACE2 expression is noticeable in certain cell types in placenta/decidua without TMPRSS2, where the viral entry depends on cathepsin B/L activity; the latter could perhaps replace TMPRSS2, since it was previously shown that SARS-CoV-2 could enter TMPRSS2-cells using cathepsin B/L [25].

4.3. Assembly and release

Following translation and production of structural proteins, nucleocapsids are assembled in the cytoplasm followed by budding into the lumen of the endoplasmic reticulum (ER)–Golgi intermediate compartment. Virions are then released from infected cell through exocytosis, where they acquire their new envelopes from the cell membrane [35].

4.4. Viral dissemination

Viruses spread from infected cells into viral-specific target uninfected cells and organs [32]. It is important to report that, the novel feature setting this virus apart from previous HCoVs is the furin cleavage site '–PRRA–' at the S1/S2 boundary of SARS-CoV-2 S, which is processed during biosynthesis [21]. This ubiquitous expression of furin-like proteases could participate in expanding SARS-CoV-2 cell and tissue tropism [21, 22]. Since, furin is expressed in a variety of organs and tissues, including brain, lung, gastrointestinal tract, liver, pancreas and reproductive tissues, it gives the possibility for the virus to infect organs or tissues that are insensitive to other coronaviruses [22]. Likewise, it is speculated that SARS-CoV-2 S protein is capable of triggering protease-independent and receptor-dependent syncytium formation; such a mechanism might enhance virus spreading through cell-cell fusion and this might partially explain rapid progress of disease [1] (Figure 3).

5. The immune system response to COVID-19

Cytopathic viruses like SARS-CoV-2 induce injury and death of virus-infected cells and tissues as part of their replicative cycle [37]. It is proposed that SARS-CoV-2 infection severely compromises the hosts' innate immune response and ability to generate a sufficient adaptive immune response, leading to opportunistic and co-infections [38]. Appealingly, virus-induced direct cytopathic effects and viral evasion of host immune responses play major roles in disease severity [39].

The immune responses induced by SARS-CoV-2 infection are two-phased: the first one, immune defense-based protective phase during the incubation and the non-severe stages, where a specific adaptive immune response will eliminate the virus and preclude disease progression to severe stages and the second one, inflammation-driven damaging phase, where virus will propagate and infect tissues in which a protective immune response would be impaired [40].

5.1. Innate immunity

SARS-CoV-2 infection that leads to the destruction of lung cells triggers a local immune response, recruiting macrophages and monocytes that respond to the infection, release cytokines and prime adaptive T and B cell immune responses [37], while using a variety of pattern-recognition receptors (PRRs), alveolar epithelial cells and

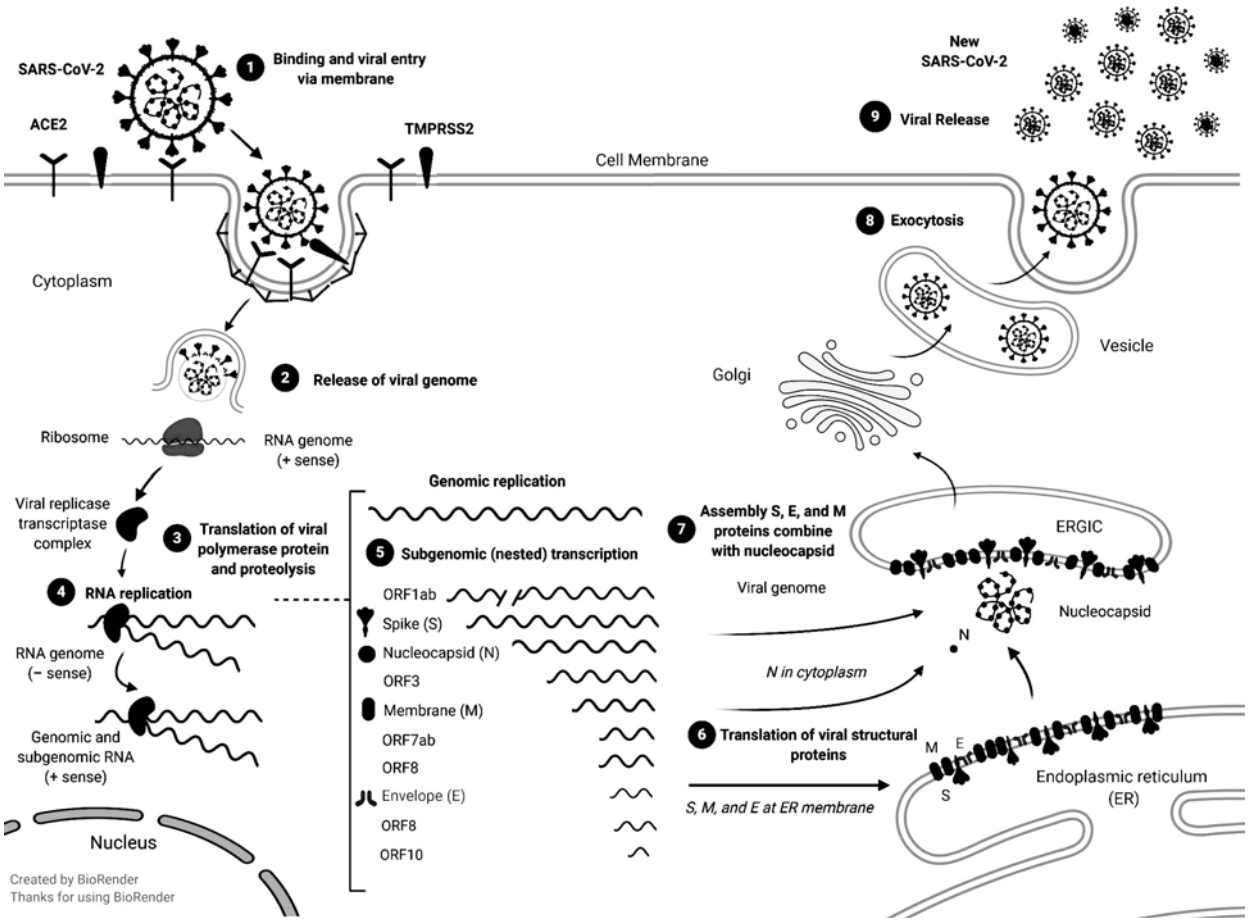

Figure 3. Schematic representation of the genomic and subgenomic organizations and replication of SARS-CoV-2. Reproduced with permission from Azkur, A. K.; Akdis, M.; Azkur, D.; Sokolowska, M.; Van de Veen, W.; Brüggen, M.; O'Mahony L.; Gao, Y.; Nadeau, K.; Akdis, C. A. Immune response to SARS- CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy* 2020, 75(7), 1564-1581 [43].

alveolar macrophages to detect the released pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs), including, the sensing of viral RNA by toll-like receptors (TLR)3, TLR7, TLR8 and TLR9 [37, 43].

Several innate immune signaling proteins are targeted by SARS-CoV-2 viral proteins; viral proteins like the Nsp13, Nsp15 and ORF9b target the interferon (IFN) pathway, and others like the Nsp13, ORF6 and ORF9c target the NF-κB pathway [43]. The ORF3b may also play a role in the viral pathogenicity by inhibiting the expression of IFNβ [44]. In particular, an effective innate immune response depends on the interferon type-I responses and downstream cascades resulting in effective induction of an adaptive immune response [38, 45].

5.2. Adaptive immunity

Adaptive immune responses to SARS-CoV-2 could be either beneficial, harmful, or both [46] (Figure 4).

5.2.1. Cell-mediated response

Upon entry into the host, the virus is recognized by antigen-presenting cells, mainly, dendritic cells and macrophages, where they hand-over after phagocytosis, viral peptides to CD4+T cells through major histocompatibility complex class 2 (MHC-class 2) molecules, but, inside the host cells, viral peptides are presented through (MHC-class 1) proteins to CD8+ cytotoxic T cells, which

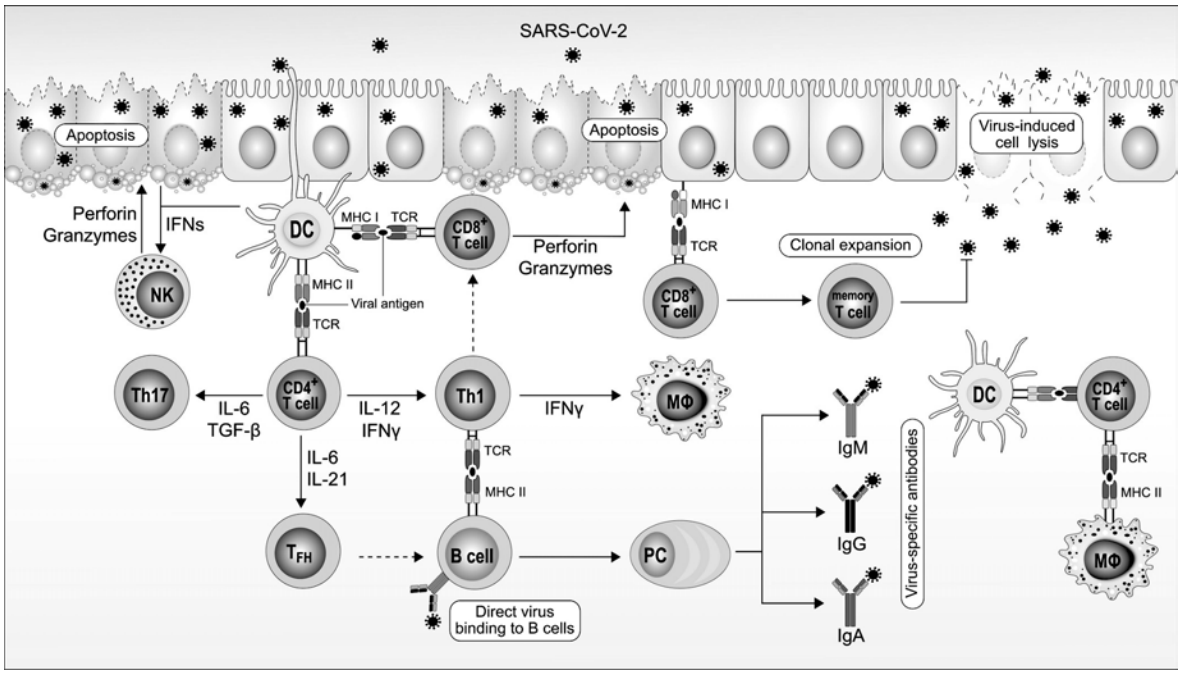

Figure 4. Immune response to SARS-CoV-2. Reproduced with permission from Azkur, A. K.; Akdis, M.; Azkur, D.; Sokolowska, M.; Van de Veen, W.; Brüggen, M.; O'Mahony L.; Gao, Y.; Nadeau, K.; Akdis, C. A. Immune response to SARS- CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy* 2020, 75(7), 1564-1581 [43].

start to divide and result in lysis of the virus-infected tissue cells [43]. Cytotoxic T-cells (CTLs) and natural killer (NK) cells are required to generate an effective immune response against viruses [38]. The CD4+ T cells advance the production of virus-specific antibodies by activating T cell-dependent B cells. However, CD8+ T cells are cytotoxic and kill the virus-infected cells [47].

The over-activation of T cells, manifested by an increase in T-helper (Th)17 cells, and the high cytotoxicity of CD8+ T cells, account for the immune injury [43]. T-helper cells make pro-inflammatory cytokines *via* NF-kB signaling, that recruit monocytes and neutrophils to the infection site showing inflammation and activates other downstream cascades of cytokines and chemokines [47]. Pulmonary recruitment of immune cells from the blood and the infiltration of lymphocytes into the airways may explain the lymphopenia seen in most COVID-19 positive patients [37].

The severe infection tends to have a central memory phenotype with a significantly higher frequency of polyfunctional CD4+T and CD8+T cells with cytokine secretion [48], where significant CD4+T cell responses were directed against nsp3, nsp4, ORF3s, ORF7a, nsp12, ORF8, nsp6, ORF3a, and the N protein for CD8+ T cell responses. It is most likely that an early CD4+ and CD8+ T cell response against SARS-CoV-2 is protective, but an early response is difficult to generate because of efficient innate immune evasion mechanisms of SARS-CoV-2 in humans [46].

5.2.2. Humoral response

The production of neutralizing antibody (NAbs) plays a protective role in limiting the infection at a later phase and prevents re-infection [45, 48]. Antibody responses to acute viral infections are typically induced in COVID-19-positive patients [49]. Usually, the viral load profile peaks at around the time of symptom onset, at 10 days or later [37, 50], and an increase in virus-specific IgM in the acute phase followed by an increase in virus-specific IgG at later phases against SARS-CoV-2 nucleoprotein (NP) or receptor-binding domain (RBD) has been observed [43, 48]. B cell

responses in patients with COVID-19 occur concomitantly with T follicular helper cell responses, from around 1 week after symptom onset, and neutralizing antibody responses, likely against the S protein, begin to develop by the 2nd week [37].

5.3. The cytokine release syndrome (CRS) "Cytokin Storm"

In most COVID-19 patients, recruited cells clear the infection in the lung, the immune response recedes and patients recover. However, in some patients, a dysfunctional immune response occurs [37], triggering higher expression of pro-inflammatory cytokines and chemokines, including IL-2, IL-7, IL10, IP- 10, TNF-α, G-CSF, MCP-1, MIP-1A, both with, the consumption of CD4+/ CD8+ T/NK cells, and the decrease in regulatory T cells, following an immune suppression stage, resulting in aggravated inflammatory responses and producing a cytokine storm [38, 39].

This concurrence of a "cytokine storm" that triggers a violent attack by the immune system on the body, with lymphopenia could underlie ARDS, viral sepsis, inflammatory damage of the lung and multi-organ failure and finally lead to death [38, 40, 45].

5.4. Immune evasion

Previous studies suggested that coronaviruses use conformational masking and glycan shielding to limit recognition by the immune response of infected hosts [21]. COVID-19 patients frequently manifest a lymphopenia, suggesting that cellular immune responses may be suppressed [41]. According to the increase in Neutrophil-to-Lymphocyte Ratio (NLR) and T lymphopenia and a decrease in CD4+ T cells with no significant change in the number of CD8+ cells and B cells, it was suggested that the COVID-19 virus might damage lymphocytes, especially T lymphocytes, and the immune system is impaired during the period of disease [39]. Interestingly, it has been shown that SARS-CoV-2 infects human T cell lines by the spike protein *via* a novel route through CD147 present on the surface of T-cells expressed in many tissues and cells, which play a role in cell proliferation, apoptosis, tumor cell migration, metastasis and differentiation, especially under hypoxic conditions [42, 43].

6. Conclusion

SARS-CoV-2 and related coronaviruses are characterized by glycoprotein spikes on their surface, which give them their appearance that resembles the corona during a total solar eclipse, which the virus uses to bind to a host cell receptor. SARS-CoV-2 binds to ACE2 receptor, which triggers a series of signaling cascades and potentially leads to different adverse outcomes. In addition to the ACE2 receptor, the virus also needs the cofactor TMPRSS2, an enzyme that forms a complex with the ACE2 receptor, to be able to penetrate the cell. The high prevalence of these receptors in the human body at so many levels correlates with the high morbidity and mortality rates in patients with COVID-19, and the lack of effective treatments makes them a worldwide challenge.

FUNDING

No source of funding.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

REFERENCES

1. Ou, X., Liu, Y., Lei, X., Li, P., Mi, D., Ren, L., Guo, L., Guo, R., Chen, T., Hu, J., Xiang, Z., Mu, Z., Chen, X., Chen, J., Hu, K., Jin, Q., Wang, J. and Qian, Z. 2020, Nat. Commun., 11(1), 1620.
2. Tsiambas, E., Papanikolaou, V., Chrysovergis, A., Mastronikolis, N., Ragos, V., Kavantzas, N., Lazaris, A. C. and Kyrodimos, E. 2020, Pathol. Oncol. Res., doi:10.1007/s12253-020-00810-6.
3. Stawiski, E. W., Diwanji, D., Suryamohan, K., Gupta, R., Fellouse, F. A., Sathirapongsasuti, J. F., Liu, J., Jiang, Y.-P., Ratan, A., Mis, M., Santhosh, D., Somasekar, S., Mohan, S., Phalke, S., Kuriakose, B., Antony, A., Junutula, J. R., Schuster, S. C., Jura, N. and Seshagiri, S. 2020, bioRxiv, 024752 [Preprint].
4. Prates, E. T., Garvin, M. R., Pavicic, M., Jones, P., Shah, M., Alvarez, C., Kainer, D., Demerdash, O., Amos, B. K., Geiger, A., Pestian, J., Jin, K., Mitelpunkt, A., Bardes, E., Aronow, B. and Jacobson, D. 2020, bioRxiv, 028712 [Preprint].

5. Wu, D., Wu, T., Liu, Q. and Yang, Z. 2020, Int. J. Infect. Dis., 94, 44-48.
6. Andersen, K. G., Rambaut, A., Lipkin, W. I., Holmes, E. C. and Garry, R. F. 2020, Nat. Med., 26(4), 450-452.
7. Prabhakar, H., Mahajan, C. and Kapoor, I. 2020, Anesth. Analg., 10, 1213.
8. Chen J. 2020, Microbes Infect., 22(2), 69-71.
9. Yang, H.-C., Chen, C., Wang, J.-H., Liao, H.-C., Yang, C.-T., Chen, C.-W., Lin, Y.-C., Kao, C.-H. and Liao, J. C. 2020, bioRxiv, 055863 [Preprint].
10. Yan, Y., Shin, W. I., Pang, Y. X., Meng, Y., Lai, J., You, C., Zhao, H., Lester, E., Wu, T. and Pang, C. H. 2020, Int. J. Environ. Res., 17(7), 2323.
11. Li, X., Geng, M., Peng, Y., Meng, L. and Lu, S. 2020, J. Pharm. Anal., 10(2), 102-108.
12. Akram, A. and Mannan, N. 2020, Bangladesh J. Infect.Dis., 7, S36-S40.
13. Anastasopoulou, S. and Mouzaki, A. 2020, Achaiki Iatriki, 39(1), 29-35.
14. Jogalekar, M. P., Veerabathini, A. and Gangadaran, P. 2020, Exp. Biol. Med., 245(11), 964-969.
15. Romano, M., Ruggiero, A., Squeglia, F., Maga, G. and Berisio, R. 2020, Cells, 9(5), 1267.
16. Helmy, Y. A., Fawzy, M., Elaswad, A., Sobieh, A., Kenney, S. P. and Shehata, A. A. 2020, J. Clin. Med., 9(4), 1225.
17. Tang, X., Wu, C., Li, X., Song, Y., Yao, X., Wu, X., Duan, Y., Zhang, H., Wang, Y. and Qian, Z. 2020, Natl. Sci. Rev., 7(6), 1012-1023.
18. Pillaiyar, T., Meenakshisundaram, S. and Manickam, M. 2020, Drug Discov., 25(4), 668-688.
19. Gu, J., Han, B. and Wang, J. 2020, Gastroenterology, 158(6), 1518-1519.
20. Letko, M., Marzi, A. and Munster, V. 2020, Nat. Microbiol., 5(4), 562-569.
21. Walls, A. C., Park, Y.-J., Tortorici, M. A., Wall, A., McGuire, A. T. and Veesler, D. 2020, Cell, 180(2), 281-292.
22. Wang, Q., Qiu, Y., Li, J.-Y., Zhou, Z.-J., Liao, C.-H. and Ge, X.-Y. 2020, Virol. Sin., 35(3), 337-339.
23. Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N.-H. and Nitsche, A. 2020, Cell, 181(2), 271-280.
24. Lan, J., Ge, J., Yu, J., Shan, S., Zhou, H., Fan, S., Zhang, Q., Shi, X., Wang, Q., Zhang, L. and Wang, X. 2020, Nature, 581(807), 215-220.
25. Sungnak, W., Huang, N., Bécavin, C., Berg, M., Queen, R., Litvinukova, M., Talavera-López, C., Maatz, H. and Reichart, D. 2020, Nat. Med., 26(5), 681-687.
26. Valencia, D. N. 2020, Cureus, 12(3), e7386.
27. Yan, R., Zhang, Y., Li, Y., Xia, L., Guo, Y. and Zhou, Q. 2020, Science, 367(6485), 1444-1448.
28. Xia, S., Lan, Q., Su, S., Wang, X., Xu, W., Liu, Z., Zhu, Y., Wang, Q., Lu, L. and Jiang, S. 2020, Signal Transduct. Target. Ther., 5(1), 92.
29. Banerjee, S., Dhar, S., Bhattacharjee, S. and Bhattacharjee, P. 2020, bioRxiv, 2020.04.06.027854 [Preprint].
30. Oberemok, V. V., Laikova, K. V., Yurchenko, K. A., Fomochkina, I. I. and Kubyshkin, A. V. 2020, Inflamm. Res., 69(7), 635-640.
31. Ma, R. C. W. and Holt, R. I. G. 2020, Diabet. Med., 37(5), 723-725.
32. Xiao, F., Tang, M., Zheng, X., Liu, Y., Li, X. and Shan, H. 2020, Gastroenterology, 158(6), 1831-1833.
33. Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauerhering, L., Becker, S., Rox, K. and Hilgenfeld, R. 2020, Science, 368(6489), 409-412.
34. Jin, Y., Yang, H., Ji, W., Wu, W., Chen, S., Zhang, W. and Duan, G. 2020, Viruses, 12(4), 372.
35. Abdulamir, A. S. and Hafidh, R. R. 2020, Electron. J. Gen. Med., 17(4), em202.
36. Daniel, Y., Hunt, B., Retter, A., Henderson, K., Wilson, S., Sharpe, C. and Shattock, M. 2020, Br. J. Haematol., 190(3), e126-e127.
37. Tay, M. Z., Poh, C. M., Rénia, L., MacAry, P. A. and Ng, L. F. P. 2020, Nat. Rev. Immunol., 20(6), 363-374.
38. Yaqinuddin, A. and Kashir, J. 2020, Med. Hypotheses, 140, 109777.

39. Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., Xie, C., Ma, K., Shang, K., Wang, W. and Tian, D.-S. 2020, Clin. Infect. Dis., 71(15), 762-768.
40. Shi, Y., Wang, Y., Shao, C., Huang, J., Gan, J., Huang, X., Bucci, E., Piacentini, M., Ippolito, G. and Melino, G. 2020, Cell Death and Differ., 27(5), 1451-1454.
41. Raoult, D., Zumla, A., Locatelli, F., Ippolito, G. and Kroemer, G. 2020, Cell Stress, 4(4), 66-75.
42. Wang, X., Xu, W., Hu, G., Xia, S., Sun, Z., Liu, Z., Xie, Y., Zhang, R., Jiang, S. and Lu, L. 2020, Cell. Mol. Immunol., doi:10.1038/ s41423-020-0424-9.
43. Azkur, A. K., Akdis, M., Azkur, D., Sokolowska, M., Van de Veen, W., Brüggen, M., O'Mahony, L., Gao, Y., Nadeau, K. and Akdis, C. A. 2020, Allergy, 75(7), 1564-1581.
44. Yi, Y., Lagniton, P. N. P., Ye, S., Li, E. and Xu, R.-H. 2020, Int. J. Biol. Sci., 16(10), 1753-1766.
45. Prompetchara, E., Ketloy, C. and Palaga, T. 2020, Asian Pac. J. Allergy Immunol., 38, 1-9.
46. Grifoni, A., Weiskopf, D., Ramirez, S. I., Mateus, J., Dan, J. M., Moderbacher, C. R., Rawlings, S. A., Sutherland, A., Premkumar, L., Jadi, R. S. Marrama, D., de Silva, A. M., Frazier, A., Carlin, A. F., Greenbaum, J. A., Peters, B., Krammer, F., Smith, D. M., Crotty, S. and Sette, A. 2020, Cell, 181, 1-13.
47. Vellingiri, B., Jayaramayya, K., Iyer, M., Narayanasamy, A., Govindasamy, V., Giridharan, B., Ganesan, S., Venugopal, A., Venkatesan, D., Ganesan, H., Rajagopalan, K., Rahman, P. K. S. M., Cho, S.-G., Kumar, N. S. and Subramaniam, M. D. 2020, Sci. Total Enviro., 725, 138277.
48. Rokni, M., Ghasemi, V. and Tavakoli, Z. 2020, Rev. Med. Virol., 30(3), e2107.
49. Zhao, J., Yuan, Q., Wang, H., Liu, W., Liao, X., Su, Y., Wang, X., Yuan, J., Li, T., Li, J., Qian, S., Hong, C., Wang, F., Liu, Y., Wang, Z., He, Q., Li, Z., He, B., Zhang, T., Fu, Y., Ge, S., Liu, L., Zhang, J., Xia, N. and Zhang, Z. 2020, Clin. Infect. Dis., 71(16), 2027-2034.
50. To, K. K.-W., Tsang, O. T.-Y., Leung, W.-S., Tam, A. R., Wu, T.-C., Lung, D. C., Yip, C. C.-Y., Cai, J.-P., Chan, J. M.-C., Chik, T. S.-H., Lau, D. P.-L., Choi, C. Y.-C., Chen, L.- L., Chan, W.-M., Chan, K.-H., Ip, J. D., Ng, A. C.-K., Poon, R. W.-S., Luo, C.-T., Cheng, V. C.-C., Chan, J. F.-W., Hung, I. F.-N., Chen, Z., Chen, H. and Yuen, K.-Y. 2020, Lancet Infect. Dis., 20(5), 565-574.