Pak. J. Biochem. Mol. Biol., 2021, 54(1-2):14-20

Review

SARS-CoV-2 Virus Transmission Mechanism in the Human Body

M. F. Amirova*, G. İ. Azizova

Biochemistry Department, Faculty of Public Health, Azerbaijan Medical University, Baku, Azerbaijan.

*Corresponding author: email: gerayelmira@gmail.com

Abstract

Coronavirus infections have been and remains the most common form of the pandemic with considerable morbidity in recent decades. The current form of coronavirus mainly results in severe acute respiratory syndrome (SARS-CoV). Prophylaxis and treatment of SARS-CoV is the most urgent problem of medicine. However, this is impossible without knowledge of the subtle mechanisms of the virus entry into the body, stimulating organ damage and the spread of the disease. It is revealed that the spike protein of the SARS-CoV-2 virus binds to target cells through the angiotensin-converting enzyme-2 (ACE2), which forms active angiotensin II. The SARS virus can also bind to the CD147 cell receptor which is mainly located on the surface of respiratory and gastrointestinal epithelial cells and play a role in the entry routes of virus. After the attachment of the virus to the cell, the spike protein is cleaved into subunits S1 and S2 as a result of proteolysis through a transmembrane serine protease type 2. The virus then activates endocytosis. SARS-CoV-2 can damage alveocytes type I and II, as well as endothelial cells. This process leads to the expression and secretion of anti-inflammatory cytokines.

Keywords: SARS-CoV, cytokine storm, reactive oxygen forms, receptors

It is known that epidemics affect human health and the economies of countries. The last outbreaks of coronavirus infections occurred in 2002 and 2012, but they were characterized by relatively low prevalence. The following types of coronaviruses are known: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV-1, MERS-Cov, and SARS-CoV-2. The coronavirus SARS-CoV-2 has the highest virulence and susceptibility [1]. The high mortality rate and serious economic and social disadvantages have made the study of the mechanisms of this disease and therapeutic approaches the most pressing problem in medicine. Reactive oxygen forms (ROF) formed during metabolism are of great importance, as they act as messengers in the cell. It is known that ROF kinases can stimulate inflammatory signals in the cell by increasing the expression of transcription and inflammatory genes.

The coronavirus SARS-CoV caused China's severe acute respiratory syndrome in 2002-2003, and the Middle East coronavirus (MERS-CoV) in 2012 killed more than 10,000 people. Mortality was 10% in SARS-CoV and 37% in MERS-CoV [2]. In late 2019, a new strain of coronavirus was identified by the WHO as SARS-CoV-2 which caused a new severe acute respiratory syndrome (COVID-19). As for its structure, on the outside of the virus are crown-shaped glycoprotein protrusions known as spike S-protein, which is designed to bind to the target cell's surface. It has been found that spike proteins can hide from innate immunity by undergoing conformational changes. The spike protein of the SARS-CoV-2 virus binds to target cells through angiotensin-converting enzyme-2 (ACE2), which forms active angiotensin II [3]. ACE2 is mainly expressed in the gastrointestinal tract, kidneys, blood vessels, heart and lungs. The

SARS virus can also bind to the CD147 cell receptor, called BASIGIN [4]. As a result of the virus attaching to the cell, the spike protein is broken down into S1 and S2 subunits by proteolysis of the cell via trans-membrane serine protease type 2 (trans-membrane serine 2 protease, TMPRSS2). Then S1 subunit binds to ACE2, after which the complex of S1-RBD and PD-ACE2 dissociates, while the hydrophobic S2-FP (fusion peptide) peptide is released from S2, and the virus enters the target cell by activating endocytosis [5]. Then the permanent mechanism of virus development is activated: target cell organelles translate on template viral RNA, resulting in the formation of structural proteins necessary for the virus development, which start a new generation of SARS-CoV-2 virions and continue to damage new target cells. ACE2, CD147 and TMPRSS2 are the receptors sensitive to SARS-CoV-2. The upper branches located on the surface of respiratory and gastrointestinal epithelial cells are the entry routes of infection [6,7]. The products of the virus interaction with the target cell are recognized by specific Nod-receptors involved in forming the polyprotein complex, the inflammasome [8,9].

Unlike strains with low virulence, SARS-CoV-2 passing into the lower respiratory tract gains the ability to damage alveocytes type I and II, as well as endothelial cells [10]. This process results in the expression and secretion of anti-inflammatory cytokines. During the secretion of cytokines, the epithelium of alveocytes undergoes pyroptosis, and the resulting products are phagocytosed by granulocytes and tissue macrophages [11]. In this condition, neutrophils and cytotoxic T cells, along with the formed cyto- and chemokines, cause severe pulmonary pneumonia, which causes damage to lung tissue, promotes the development of edema at the site of injury, causes acute respiratory distress syndrome, and results in fibrosis [12]. The age factor aggravates the pathological process, i.e. the changes listed in the elderly are more pronounced [13-15]. By infecting the membranes of alveolar-capillary cells, SARS-CoV-2 enters the bloodstream and can damage other organs including intestines, kidneys, esophagus, heart, blood vessels, brain, bladder, etc. [16]. In the early stages of the disease, the nsp1 and rp6 proteins of the virus inhibit the formation of interferon. Vazquez et al. [17] has stated that NSP1 and NSP13 proteins of SARS-CoV-2 block activation of interferon via different mechanisms. Macrophages entering the site of inflammation continue to produce chemo-attractants for mononuclear cells, and thus their concentration increases rapidly which triggers the inflammatory process to move to the next stage, the cytokine "storm" [18-20]. At this stage, the level of inflammatory cytokines and chemo-attractants (interleukins, monocyte chemo-attractant protein MCP-1) continues to increase dramatically [21]. Moreover, levels of macrophages inflammatory protein MIP-1a, TGF, CCL2, CXCL10, CXCL9 and TNF increase sharply. The cytokines HGF and CXCL13 levels in the blood predict the severity and the mortality in SARS-CoV patients [22].

In severe cases of SARS-CoV-2 infection, there are significant changes in the acute phase proteins of the blood, and at this stage, markers such as C-reactive protein, ferritin, ceruloplasmin [23], blood clotting factors [24,25], serum enzymes indicate a failure of numerous organs. In about 82% of cases, leukopenia, thrombocytopenia and loss of eosinophils and lymphopenia are observed in peripheral blood, and sometimes leucocytes, neutrophils are increased [26]. Viral respiratory infections stimulate the inflammatory process and contribute to developing pathophysiological processes against the

background of an excess of cytokines, oxygen and nitrogen active forms. Mitochondria is the main generator of reactive oxygen forms (ROF), and along with SARS-CoV 3b protein and non-structural protein 10 (nsp10), ROFs can change the course of processes in mitochondria [27]. SARS-CoV 3b may enter mitochondria [28,29], while nsp10 may interact specifically with the NADH 4L subunit and cytochrome oxidase II [28, 27]. It has also been shown that after these interactions, the genes encoding mitochondrial DNA in peripheral blood mononuclear cells and genes sensitive to oxidative stress such as peroxiredoxin 1 [30], and the ferritin heavy chain polypeptide gene are activated. Oxidative stress increases the expression of anti-inflammatory phospholipase A2 which lowers antiviral immunity [31].

Interestingly, phospholipase A2 is naturally activated in humans [32]. The specific human protein kinase is activated by mitogens due to the damaging effects of the environment, such as oxidative stress, accumulation of DNA damage, carcinogens, and viruses. Thus, those who have a deletion of the ncf1 gene that stimulates the formation of ROF and do not have Toll-like receptor-4 (TLR4), which activates innate immunity, have a natural resistance to respiratory viruses, including the SARS COV2 virus. Imai et al. [33] observed that the oxidized phospholipid induced lung injury and cytokine production by lung macrophages via TLR4-TRIF [33]. It is also known that SARS-CoV2 3CLpro protease induces apoptosis in human promonocytes [34] by increasing the formation of ROF [35]. The occurrence of oxidative stress can lead to severe lung damage. *In vivo* oxidative stress activates 3CLpro protease and NF-kB-factor [36,37] but inhibits protein-1-dependent transcription [38]. Hence ROF-induced transmission of the 3CLpro-stimulated NF-kB signal may have played a leading role in the pathophysiology of SARS-CoV2 infection. This is due to the activation of the phosphatidylinositol-3-kinase/protein kinase pathway by various viruses during latent or chronic infections [39,40] which allows infected cells to avoid apoptosis [41]. Consequently, the virus spreads in the body.

All the data accumulated to date make it possible to correctly guide the treatment process for SARS-CoV infection and reduce the mortality among patients, prevent complications, and choose the right drugs to preserve the viability of organs and tissues. Further investigations will make the therapy and prevention of SARS-CoV infection even more accurate.

References.

1. Liu DX, Liang JQ, Fung TS. Human Coronavirus-229E, -OC43, -NL63, and -HKU1 (*Coronaviridae*). *Encyclopedia of Virology*. 2021;428-440. doi:10.1016/B978-0-12-809633-8.21501-X.
2. Liu J, Xie W, Wang Y, et al. A comparative overview of COVID-19, MERS and SARS: Review article. *Int J Surg*. 2020;81:1-8. doi:10.1016/j.ijsu.2020.07.032.
3. Ni W, Yang X, Yang D, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care*. 2020;24(1):422. Published 2020 Jul 13. doi:10.1186/s13054-020-03120-0.
4. Ragotte RJ, Pulido D, Donnellan FR, Hill ML, Gorini G, Davies H, Brun J, McHugh K, King LDW, Skinner K, Miura K, Long CA, Zitzmann N, Draper SJ. Human Basigin (CD147) Does Not Directly Interact with SARS-CoV-2 Spike Glycoprotein. mSphere. 2021 Aug 25;6(4):e0064721. DOI:

10.1128/mSphere.00647-21. Epub 2021 Aug 11. PMID: 34378982; PMCID: PMC8386461.

5. Lai AL, Freed JH. SARS-CoV-2 Fusion Peptide has a Greater Membrane Perturbating Effect than SARS-CoV with Highly Specific Dependence on Ca^2. *J Mol Biol*. 2021;433(10):166946. doi:10.1016/j.jmb.2021.166946.
6. Zang R, Gomez Castro MF, McCune BT, et al. TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes. *Sci Immunol*. 2020;5(47):eabc3582. doi:10.1126/sciimmunol.abc3582.
7. Hoffmann M., Kleine-Weber H., Schroeder S. et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor/ Cell, 2020, V. 181 (2), Apr 16: 271-280.e8.
8. Wen H, Miao EA, Ting JP. Mechanisms of NOD-like receptor-associated inflammasome activation. *Immunity*, 2013, 39(3), 432-441. doi:10.1016/j.immuni.2013.08.037
9. Tripathy S., Dassarma B., Roy S., Chabalala H., Matsabisa M. A review on possible modes of actions of Chloroquine/ Hydroxychloroquine: Repurposing against SAR-COV-2 (COVID 19) pandemic/ International Journal of Antimicrobial Agents, 2020, Aug., 56(2):106028; https://www.researchgate.net/publication/341590117A
10. Carcaterra M, Caruso C. Alveolar epithelial cell type II as main target of SARS-CoV-2 virus and COVID-19 development via NF-Kb pathway deregulation: A physio-pathological theory. Med Hypotheses. 2021 Jan;146:110412. doi: 10.1016/j.mehy.2020.110412. Epub 2020 Nov 23. PMID: 33308936; PMCID: PMC7681037.
11. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. *Eur Respir J*. 2020;55(4):2000607. Published 2020 Apr 16. doi:10.1183/13993003.00607-2020.
12. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine Growth Factor Rev*. 2020;54:62-75. doi:10.1016/j.cytogfr.2020.06.001.
13. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194-1217. doi:10.1016/j.cell.2013.05.039
14. Front. Physiol., Jan 12 2021 | https://doi.org/10.3389/fphys.2020.571416
15. Bajaj V., Gadi N., Spihlman A.P. et al. Aging, Immunity, and COVID-19: How Age Influences the Host Immune Response to Coronavirus Infections? Front. Physiol., Jan 12 2021 | https://doi.org/10.3389/fphys.2020.571416
16. Ni W, Yang X, Yang D, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care*. 2020;24(1):422. Published 2020 Jul 13. doi:10.1186/s13054-020-03120-0.
17. Vazquez C, Swanson SE, Negatu SG, Dittmar M, Miller J, Ramage HR, Cherry S, Jurado KA. SARS-CoV-2 viral proteins NSP1 and NSP13 inhibit interferon activation through distinct mechanisms. PLoS One. 2021 Jun 24;16(6):e0253089. doi: 10.1371/journal.pone.0253089.

PMID: 34166398; PMCID: PMC8224853.

18. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine Growth Factor Rev*. 2020;54:62-75. doi:10.1016/j.cytogfr.2020.06.001.
19. Jafarzadeh A, Chauhan P, Saha B, Jafarzadeh S, Nemati M. Contribution of monocytes and macrophages to the local tissue inflammation and cytokine storm in COVID-19: Lessons from SARS and MERS, and potential therapeutic interventions. *Life Sci*. 2020;257:118102. doi:10.1016/j.lfs.2020.118102.
20. Song P, Li W, Xie J, Hou Y, You C. Cytokine storm induced by SARS-CoV-2. Clin Chim Acta. 2020 Oct;509:280-287. doi: 10.1016/j.cca.2020.06.017. Epub 2020 Jun 10. PMID: 32531256; PMCID: PMC7283076.
21. Xi, X., Guo, Y., Zhu, M. *et al.* Higher expression of monocyte chemotactic protein 1 in mild COVID-19 patients might be correlated with inhibition of Type I IFN signaling. *Virol J* 18, 12 (2021). https://doi.org/10.1186/s12985-020-01478-9.
22. Perreau, M., Suffiotti, M., Marques-Vidal, P. *et al.* The cytokines HGF and CXCL13 predict the severity and the mortality in COVID-19 patients. *Nat Commun* 12, 4888 (2021). https://doi.org/10.1038/s41467-021-25191-5.
23. Hackler J, Heller RA, Sun Q, Schwarzer M, Diegmann J, Bachmann M, Moghaddam A, Schomburg L. Relation of Serum Copper Status to Survival in COVID-19. Nutrients. 2021 May 31;13(6):1898. doi: 10.3390/nu13061898. PMID: 34072977; PMCID: PMC8229409.
24. Ryu JK, Sozmen EG, Dixit K, Montano M, Matsui Y, Liu Y, Helmy E, Deerinck TJ, Yan Z, Schuck R, Acevedo RM, Spencer CM, Thomas R, Pico AR, Zamvil SS, Lynch KL, Ellisman MH, Greene WC, Akassoglou K. SARS-CoV-2 spike protein induces abnormal inflammatory blood clots neutralized by fibrin immunotherapy. bioRxiv [Preprint]. 2021 Oct 13:2021.10.12.464152. doi: 10.1101/2021.10.12.464152. PMID: 34671772; PMCID: PMC8528086.
25. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. *Ther Adv Respir Dis*. 2020;14:1753466620937175. doi:10.1177/1753466620937175.
26. Letícia de Oliveira Toledo S, Sousa Nogueira L, das Graças Carvalho M, Romana Alves Rios D, de Barros Pinheiro M. COVID-19: Review and hematologic impact. *Clin Chim Acta*. 2020;510:170-176. doi:10.1016/j.cca.2020.07.016.
27. Li Q, Wang L, Dong C, et al. The interaction of the SARS coronavirus non-structural protein 10 with the cellular oxido-reductase system causes an extensive cytopathic effect. *J Clin Virol*. 2005;34(2):133-139. doi:10.1016/j.jcv.2004.12.019.
28. Varshney B, Agnihothram S, Tan YJ, Baric R, Lal SK. SARS coronavirus 3b accessory protein modulates transcriptional activity of RUNX1b. PLoS One. 2012;7(1):e29542. doi:

10.1371/journal.pone.0029542. Epub 2012 Jan 12. Erratum in: PLoS One. 2012;7(3). doi:10.1371/annotation/64ae6047-0f9b-4d17-a065-e08c153aa435. Agnihotram, Sudhakar [corrected to Agnihothram, Sudhakar]. PMID: 22253733; PMCID: PMC3257236.

29. Singh K., Chaubey G., Chen J.Y., Suravajhala P. Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis\ Cell Physiology, 20 JUL 2020, https://doi.org/10.1152/ajpcell.00224.2020
30. Zhang H., Shen, J., Xu H. et al.Activation of Peroxiredoxin 1 by Fluvastatin Effectively Protects from Inflammation and SARS-CoV-2. Available at SSRN: https://ssrn.com/abstract=3606782 or http://dx.doi.org/10.2139/ssrn.3606782.
31. Snider J.M., Karen J.Y., Wang X.Group IIA secreted phospholipase A_2 is associated with the pathobiology leading to COVID-19 mortality. J.Clin.Investigation https://www.jci.org/articles/view/149236
32. Yamamoto K, Gelb M, Murakami M, Perlman S. Critical role of phospholipase A2 group IID in age-related susceptibility to severe acute respiratory syndrome-CoV infection. J Exp Med. 2015 Oct 19;212(11):1851-68. doi: 10.1084/jem.20150632. Epub 2015 Sep 21. PMID: 26392224; PMCID: PMC4612096.
33. Imai Y, Kuba K, Neely GG, et al. Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. *Cell*. 2008;133(2):235-249. doi:10.1016/j.cell.2008.02.043.
34. Lai CC, Jou MJ, Huang SY, Li SW, Wan L, Tsai FJ, Lin CW. Proteomic analysis of up-regulated proteins in human promonocyte cells expressing severe acute respiratory syndrome coronavirus 3C-like protease. Proteomics. 2007 May;7(9):1446-60. doi: 10.1002/pmic.200600459. PMID: 17407183; PMCID: PMC7167764.
35. Forcados G.E., Muhammad A., Oladipo O.O. et al. Metabolic Implications of Oxidative Stress and Inflammatory Process in SARS-CoV-2 Pathogenesis: Therapeutic Potential of Natural Antioxidants REVIEW article. Front. Cell. Infect. Microbiol., May 26 2021 | https://doi.org/10.3389/fcimb.2021.654813.
36. Meftahi G.H., Bahari Z., Jang Z., Iman M. A vicious circle between oxidative stress and cytokine storm in acute respiratory distress syndrome pathogenesis at COVID - 19 infection Ukr. Biochem. J., 2021, Vol. 93, N 1. doi: https://doi.org/10.15407/ubj93.01.018.
37. Morgan MJ, Liu ZG. Crosstalk of reactive oxygen species and NF-κB signaling. *Cell Res*. 2011;21(1):103-115. doi:10.1038/cr.2010.178.
38. Shi Q, Gibson GE. Oxidative stress and transcriptional regulation in Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2007;21(4):276-291. doi:10.1097/WAD.0b013e31815721c3.
39. Mizutani T, Fukushi S, Saijo M, Kurane I, Morikawa S. Importance of Akt signaling pathway for apoptosis in SARS-CoV-infected Vero E6 cells. Virology. 2004 Oct 1;327(2):169-74. doi: 10.1016/j.virol.2004.07.005. PMID: 15351204; PMCID: PMC7111732.

40. Krystal GW, Sulanke G, Litz J. Inhibition of phosphatidylinositol 3-kinase-Akt signaling blocks growth, promotes apoptosis, and enhances sensitivity of small cell lung cancer cells to chemotherapy. Mol Cancer Ther. 2002 Sep;1(11):913-22. PMID: 12481412.

41. Yao R, Cooper GM. Requirement for phosphatidylinositol-3 kinase in the prevention of apoptosis by nerve growth factor. Science. 1995 Mar 31;267(5206):2003-6. doi: 10.1126/science.7701324. PMID: 7701324.