University of Thi-Qar Journal of Science (UTJsci)
E-ISSN:2709-0256, ISSN Print: 1991-8690 Volume (10), No.1 June 2023

The role of Interleukin-6 (IL-6) in pathogensis of COVID -19

Noorulhuda F. Khalaf
Tropical Biological Research Unit/College of Science/ University of Baghdad
Baghdad/ Iraq
https://orcid.org/0000-0001-9958-1797

Sinai W. Mohammed
Tropical Biological Research Unit /College of Science/University of Baghdad
Baghdad/ Iraq
https://orcid.org/0000-0001-8359-4921

Ahmed Y. Hanoon
Tropical Biological Research Unit/College of Science/University of Baghdad
Baghdad/ Iraq

Abstract---**Dissimilar to all other pandemics in the past five decades, the humanity has been ravaged by the coronavirus disease COVID-19. Starting from its outbreak, the disease's understanding has advanced quickly; multi-organ involvement is the key factor affecting the prognosis of the disease. Mortality and morbidity are closely related to acute respiratory distress syndrome, renal failure, cardiac failure, liver damage, multi-organ failure, and shock. In the initial phases of viral infection, detecting and controlling pro-inflammatory responses are essential. Throughout patient monitoring, it is crucial to consider the COVID-19 treatment's unknowable response. It has been discovered that interleukin-6 (IL-6) is causally linked to greater mortality. It is a reliable indicator regarding the progression of clinical profile as well as the prognosis of the disease. A highly important cytokine, after the activated macrophages, is it. As a result, a measure for COVID-19 could be the control regarding systemic IL-6 levels in the individuals that have been infected by SARS-CoV-2. This study has demonstrated the significance of IL-6 in COVID-19's immunopathology.**

Keywords: *COVID-19, Cytokines, IL-6, Pathogenesis*

I. INTRODUCTION

A respiratory infection is brought on by coronaviruses, members of the Coronaviridae family, in both avian and mammal species, including camels, bats, and masked palm civets (1). Diverse host species may exhibit various coronavirus infection symptoms as well as tissue tropism (2). Human coronavirus infections can be asymptomatic or come with symptoms like coughing, fever, stomach discomfort, and shortness of breath (3). In some situations, especially in immunocompromised and old people, coronavirus infections can cause severe pneumonia and ultimately the patient's death (4). The WHO designated COVID-19, which is caused by SARS-CoV-2, as pandemic on March 11th, 2020. All over the globe, about 496 million confirmed cases and more than 6 million fatalities were documented as of 10 April 2022 (5). SARS-CoV-2 can be defined as a brand-new coronavirus strain which hasn't been found in the humans before. SARS-CoV-2 may have evolved from the zoonotic cycle and expanded quickly through human-to-human transmission, according to phylogenetic study (6). Cytokines are thought to be crucial in controlling and treating coronavirus infections throughout SARS-CoV-2 infection. Yet, unchecked and excessive cytokine production can cause tissue damage across the whole human body, which can result in immunopathogenesis (7). Patients with COVID-19 will experience some mild to moderate symptoms, however a few infected individuals could experience cytokine release syndrome (CRS), which is a hyper-inflammation that is brought on by large cytokine/chemokine production that can cause deadly pneumonia and acute respiratory distress syndrome. An essential cytokine, IL-6 is associated with a number of inflammatory disorders. High amounts of IL-6 were found in SARS-CoV-2-infected subjects, and these levels have been linked to patient symptoms like severe lung damage and pulmonary inflammation (8). Patients who had SARS-CoV2 also exhibited low levels of cytokine signaling-3suppressor that controls and boosts IL-6's negative feedback mechanism (9). In the same line, another research found that severe COVID-19 patients had greater IL-6 levels, and this could be one of bases to predict change from a mild infection to severe one (10).

II. PATHOGENESIS of SARS-CoV-2

Understanding the pathogenesis of COVID-19, which is spreading quickly and causing significant morbidity and mortality all over the world, will be crucial for managing it. The primary receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2), which is found in vascular, respiratory epithelium, macrophages, and alveolar monocytes. Another significant COVID-19 pandemic symptom was lymphopenia. The loss of CD8 and CD4 cells, a hallmark of SARS-CoV-2 patients, frequently came before the disease's radiographic manifestations. Unknown

https://doi.org/10.32792/utq/utjsci/v10i1.895

mechanisms underlie the increasing lymphopenia in patients with critical and severe COVID-19. According to studies, increased mortality in patients with this disease is associated with a lower lymphocyte count and higher ferritin, D-dimer, and IL-6 levels. The three phases of the SARS-CoV-2 infection's clinical course include the viremia phase, the acute phase (pneumonia), and the severity or recovery phases. The early interventions have mostly been centered on the proper timing of disease phases and the implementation of strategies to halt or decrease the progression in COVID-19 patients. The steps in viral entry, replication, and appearance of viral protein (spike protein) on the host cell surface facilitated activation of the innate immune system through inflammatory signaling pathways such as cytokine production and programmed cell death (11, 12) (Fig.1).

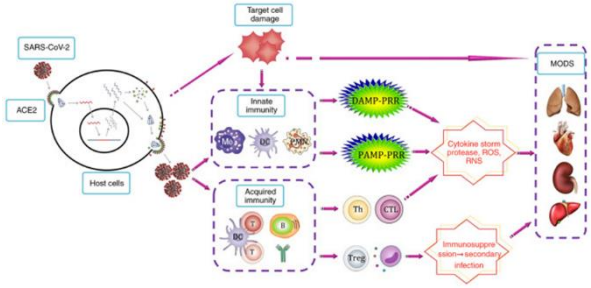

Figure 1: Hypothetical pathogenesis of COVID-19 [11].

III. CYTOKINES & COVID-19

The interesting point in COVID-19 patients is the cytokine storm. Patients with COVID-19 who had more severe disease showed high levels of inflammatory cytokines, which were linked to lung damage, pulmonary inflammation, and multiple organ failure (13). The increase in serum levels of pro-inflammatory cytokines like IL6, IL1, IFN, IL12, MCP1, and IP10 was linked to pulmonary inflammation in SARS patients, according to prior research [14]. activated T-helper-1 (Th-1) cell response is likely the result of increased IFNγ, IL1-β, IP-10, and MCP-1 levels in ICU COVID-19 patients, according to Huang *et al.* report (15). Additionally, Diao *et al.* discovered a correlation between severity of COVID-19 and TNF-α, IL-10, and IL-6levels (16).

IV. INTERLEUKIN-6 (IL-6)

One of the major key mediators regarding inflammation and viral cytokine storm in COVID-19 patients is IL6 (17). Also, IL-6 can be defined as a cytokine that regulates cell differentiation and proliferation as well as the immune response. A 28-amino-acid signal peptide makes up part of the 212 amino acids . The human IL-6 gene is located on chromosome 7p21. A cytokine called IL-6 has both anti- and pro-inflammatory characteristics. Additionally, IL-6 secretion has been linked to a number of other diseases and conditions, including Alzheimer's, atherosclerosis, multiple myeloma, systemic lupus erythematosus, autoimmune deficiency disease, rheumatoid arthritis, chronic inflammatory disease, and various cancers. Thus, throughout disease, particularly their activation following immune response triggering, control of IL-6 secretion has been found to be especially crucial (18, 19).

A. SOURCES OF IL-6 PRODUCTION

Numerous types of cells, which include the macrophages, fibroblasts, T cells, endothelial cells, and monocytes, release IL-6 (20). The T cells, B cells, eosinophils, basophils, and neutrophils are targets of IL6. The differentiation regarding β cells and the production of IgE, IgM, and IgA are two activities of IL-6 on the β cells. IL-6 also regulates differentiation, survival, and activation of the T cells. In response to interleukin, leukocytes are activated. Thus, cytokine storm after infection results in B and T cell differentiation and activation. Cancers with poor prognoses or cancer that has spread to other organs have higher levels of IL-6. IL-6 secretion increases auto-antibody hyper gamma globulinemia and induces B cells to produce antibodies. IL-6 also results in autoimmunity, chronic inflammation, CD-4 positive T-cell activation that promotes the differentiation of theTh-17, and the CD-4 positive T-cell inhibition that prevents the differentiationof the Treg (21).

B. IL-6 AND VIRAL INFECTIONS

Following viral infection, viral products promote the translation or transcription of IL-6 as well from the cells like mesenchymal, fibroblast, endothelial, and various other cell types. Inhibition of IL6's signal that impacts cells could thus depend on the control of IL6 secretion and synthesis. Negatively regulating the IL-6 transcription also involves using techniques that suppress IL-6 expression (22, 23). Following viral infection, the activation regarding IL-6 and the release of additional cytokines results in a fatal immune response to the hyper-activation of the T cells. The similar cytokine storm is seen as well following cancer treatment as a result of the activation of the T-cells and an increase in the secretion of the IL-6. As a result, it is believed that pathological IL6 secretion is to blame for clinical symptoms that follow a severe disease (24).

C. IL-6 IN PATHOGENESIS OF COVID -19

The link between the levels of IL-6 and virus pathogenicity can be seen in the systemic elevation of IL6 throughout acute stage of the viral infections. Pleotropic cytokine IL-6 is generated in response to the tissue injury and infections. Additionally, compared to virus-negative groups, human patients with virus infections had higher levels of circulating IL-6, MCP-1 and TNF-α (25, 26). Due to the fact that secretion of IL-6 that is produced from several types of

cell begins the activation pathway of the JAK/STAT3, it leads to the promotion of numerous factors of transcription that are related to the processes of the cellular signalling. Due to the fact that it regulates monocyte differentiation to macrophages, boosts the production of the β-cell IgG, and promotes Th-2 response through suppressing the polarization of theTh1, IL6 has been regarded as a very crucial cytokine throughout an infection (27). Since IL-6 production was linked to both anti- and pro-inflammatory effects, more research is required to understand how IL-6 mediates the cellular response to the viral infections, particularly coronavirus.

D. IL-6 AS POTENTIAL THERAPEUTIC TARGET FOR COVID -19

Depending on its ability to block cytokine storms, a few works have suggested that humanized monoclonal antibody against the IL6 receptors, tocilizumab, could be utilized in the treatment of coronavirus (28). Tocilizumab can be defined as an IL-6 receptor antagonist utilized for treating CRS (29). In 21 patients with severe COVID-19 infection, one of the recent retrospective Chinese studies had found that the tocilizumab reduced fever, hypoxemia, and levels of CRP without having any severe negative effects (30). Tocilizumab might just be administered to COVID-19 patients that are at the end of phase of high viral load, have severe respiratory failures, interstitial pneumonia, and high levels of lL6 and/or C-reactive protein/D-dimer/fibrinogen/ferritin, according to Italian recommendations (31). Cytokine storm can be treated with immunosuppressants and corticosteroids, and it is systemic in patients with COVID-19. Using hydrocortisone, however, has been linked to COVID-19 patients' slower viral clearance and a greater plasma SARS-CoV2 viral load, according to recent investigations (32).

V. CONCLUSION

Clinical practice must constantly take into account IL-6's crucial function in host defense. For patients with a variety of clinical symptoms, different algorithms are utilized throughout COVID-19 therapy. Yet, it is unclear how the treatment will react to the cytokine storm, particularly the release of IL-6. Increased systemic IL-6 levels must be required to determine a higher probability of disease deterioration based on COVID-19 severity. As a result, targeting IL-6 treatment for patients who have been tested positive for COVID-19 or monitoring IL-6 levels could be a new effective treatment target.

VI. REFERENCES

[1] A. Sharma, I. Ahmad Farouk, and S. K. Lal, "COVID-19: A Review on the Novel Coronavirus Disease Evolution, Transmission, Detection, Control and Prevention," Viruses, vol. 13, no. 2, p. 202, Jan. 2021, doi: 10.3390/v13020202. [Online]. Available: http://dx.doi.org/10.3390/v13020202.

[2] A. R. Fehr and S. Perlman, "Coronaviruses: An Overview of Their Replication and Pathogenesis," in Coronaviruses: Methods and Protocols, H. J. Maier, E. Bickerton, and P. Britton, Eds. New York, NY: Springer New York, 2015, pp. 1–23. https://doi.org/10.1007/978-1-4939-2438-7_1.

[3] N. Chen et al., "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study," Lancet, vol. 395, no. 10223, pp. 507–513, 2020, https://doi.org/10.1016/S0140-6736(20)30211-7.

[4] L. Jartti, "New Respiratory Viruses and the Elderly," Open Respir. Med. J., vol. 5, no. 1, pp. 61–69, 2011, https://doi.org/10.2174/1874306401105010061.

[5] W. H. Organization, "Laboratory testing of 2019 novel coronavirus (2019-nCoV) in suspected human cases: interim guidance, 17 January 2020," 2020. [Online]. Available: https://www.who.int/publications/i/item/laboratory-testing-of-2019-novel-coronavirus-(-2019-ncov)-in-suspected-human-cases-interim-guidance-17-january-2020

[6]J. F. W. Chan et al., "A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster," Lancet, vol. 395, no. 10223, pp. 514–523, 2020, doi: 10.1016/S0140-6736(20)30154-9.

[7] P. Mehta, D. F. McAuley, M. Brown, E. Sanchez, R. S. Tattersall, and J. J. Manson, "COVID-19: consider cytokine storm syndromes and immunosuppression," Lancet, vol. 395, no. 10229, pp. 1033–1034, 2020, doi: 10.1016/S0140-6736(20)30628-0.

[8] R. Lu et al., "Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding," Lancet, vol. 395, no. 10224, pp. 565–574, 2020, doi: 10.1016/S0140-6736(20)30251-8.

[9] T. Okabayashi et al., "Cytokine Regulation in SARS Coronavirus Infection Compared to Other Respiratory Virus Infections," vol. 424, pp. 417–424, 2006, doi: 10.1002/jmv.

[10] F. Wang et al., "Characteristics of Peripheral Lymphocyte Subset Alteration in COVID-19 Pneumonia," vol. 221, no. 1, 2020, doi: 10.1093/infdis/jiaa150.

[11] A. Bahrami and G. A. Ferns, "Genetic and pathogenic characterization of SARS-CoV-2: A review," Future Virol.,

vol. 15, no. 8, pp. 533–549, 2020, doi: 10.2217/fvl-2020-0129.

[12] W. Cao and T. Li, "COVID-19: towards understanding of pathogenesis," Cell Res., vol. 30, no. 5, pp. 367–369, 2020, doi: 10.1038/s41422-020-0327-4.

[13] R. Channappanavar and S. Perlman, "Pathogenic human coronavirus infections : causes and consequences of cytokine storm and immunopathology," pp. 529–539, 2017, doi: 10.1007/s00281-017-0629-x.

[14] C. K. Wong et al., "Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome," Clin. Exp. Immunol., vol. 136, no. 1, pp. 95–103, 2004, doi: 10.1111/j.1365-2249.2004.02415.x.

[15] C. Huang et al., "Clinical features of patients infected with 2019 novel coronavirus in Wuhan , China," Lancet, vol. 395, pp. 497–506, 2020, doi: 10.1016/S0140-6736(20)30183-5.

[16] B. Diao et al., "Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19)," Front. Immunol., vol. 11, no. May, pp. 1–7, 2020, doi: 10.3389/fimmu.2020.00827.

[17] D. W. Lee et al., "Current concepts in the diagnosis and management of cytokine release syndrome," Blood, vol. 124, no. 2, pp. 188–195, 2014, doi: 10.1182/blood-2014-05-552729.

[18] P. C. Heinrich, J. V. Castell, and T. Andus, "Interleukin-6 and the acute phase response," Biochemical Journal, vol. 265, no. 3. pp. 621–636, 1990. doi: 10.1042/bj2650621.

[19] H. Kumar, T. Kawai, and S. Akira, "Pathogen Recognition by the Innate Immune System," Int. Rev. Immunol., vol. 30, no. 1, pp. 16–34, 2011, doi: 10.3109/08830185.2010.529976.

[20] M. Narazaki and T. Kishimoto, "The two-faced cytokine IL-6 in host defense and diseases," International Journal of Molecular Sciences, vol. 19, no. 11. 2018. doi: 10.3390/ijms19113528.

[21] S. Qian et al., "Transmissible Gastroenteritis Virus Infection Up-Regulates FcRn Expression via Nucleocapsid Protein and Secretion of TGF-β in Porcine Intestinal Epithelial Cells," Front. Microbiol., vol. 10, no. January, pp. 1–12, 2020, doi: 10.3389/fmicb.2019.03085.

[22] A. Ray and K. E. Prefontaine, "Physical association and functional antagonism between the p65 subunit of transcription factor NF-κB and the glucocorticoid receptor," Proc. Natl. Acad. Sci. U. S. A., vol. 91, no. 2, pp. 752–756, 1994, doi: 10.1073/pnas.91.2.752.

[23] P. Delerive et al., "Peroxisome proliferator-activated receptor α negatively regulates the vascular inflammatory gene response by negative cross-talk with transcription factors NF-κB and AP-1," J. Biol. Chem., vol. 274, no. 45, pp. 32048–32054, 1999, doi: 10.1074/jbc.274.45.32048.

[24] S. A. Grupp et al., "Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia," N. Engl. J. Med., vol. 368, no. 16, pp. 1509–1518, 2013, doi: 10.1056/nejmoa1215134.

[25] T. Tanaka, M. Narazaki, and T. Kishimoto, "IL-6 in Inflammation, Immunity, and Disease," Harb. Perspect. Biol., vol. 6, no. 10, pp. 1–17, 2
014, [Online]. Available: http://cshperspectives.cshlp.org

[26] J. Zheng et al., "The Expression of IL-6, TNF- μ and MCP-1 in Respiratory Viral Infection in Acute Exacerbations of Chronic Obstructive Pulmonary Disease," J. Immunol. Res., vol. 2017, pp. 1–9, 2017, doi: 10.1155/2017/8539294.

[27] L. Velazquez-Salinas, A. Verdugo-Rodriguez, L. L. Rodriguez, and M. V. Borca, "The role of interleukin 6 during viral infections," Frontiers in Microbiology, vol. 10, no. MAY. pp. 6–11, 2019. doi: 10.3389/fmicb.2019.01057.

[28] B. R. Dholaria, C. A. Bachmeier, and F. Locke, "Mechanisms and Management of Chimeric Antigen Receptor T-Cell Therapy-Related Toxicities," BioDrugs, vol. 33, no. 1. Springer International Publishing, pp. 45–60, 2019. doi: 10.1007/s40259-018-0324-z.

[29] C. Ding and G. Jones, "Technology evaluation: MRA, Chugai," Current Opinion in Molecular Therapeutics, vol. 5, no. 1. pp. 64–69, 2003.

[30] X. Xu et al., "Effective treatment of severe COVID-19 patients with tocilizumab," Proc. Natl. Acad. Sci. U. S. A., vol. 117, no. 20, pp. 10970–10975, 2020, doi: 10.1073/pnas.2005615117.

[31] I. O. Rosas et al., "Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia," N. Engl. J. Med., vol. 384, no. 16, pp. 1503–1516, 2021, doi: 10.1056/nejmoa2028700.

[32] C. D. Russell, J. E. Millar, and J. K. Baillie, "Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury," The Lancet, vol. 395, no. 10223. pp. 473–475, 2020. doi: 10.1016/S0140-6736(20)30317-2.