IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
July 2020 Vol.:18, Issue:4
© All rights are reserved by Anusha Shaji et al.

Review on Stem Cell and Their Role in the Pharmacotherapy of COVID 19

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Anu Sebastian[1], Anusha Shaji[2*], Jeethu Joby[3], Merrin Joseph[4,] Dona Maria Jetto[5]

[1,2]Assistant Professor, Department of Pharmacology, Nirmala College of Pharmacy, Ernakulam, Kerala, India
[3,4,5]Assistant Professor, Department of Pharmacy Practice, Nirmala College of Pharmacy, Ernakulam, Kerala, India

Submission: 20 June 2020
Accepted: 27 June 2020
Published: 30 July 2020

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Stem Cells, COVID 19, Adult and Mesenchymal stem cells, Corona Virus, n-COV-19

ABSTRACT

COVID-19 causes a cytokine storm in the body, that is, virus-activated immune cells exude an excess of cellular hormones (cytokines) that have detrimental effects on their own tissues, endorse swelling, fibrosis (growth of connective tissue) and functional insufficiency. Mesenchymal stem cells are a powerful immunomodulatory and anti-inflammatory agent, they normalize the function of the immune system, changed by COVID-19. The anti-inflammatory effect of mesenchymal stem cells has been known for a long time that is why they have been successfully used for over 10 years in the treatment of autoimmune diseases (rheumatoid arthritis, ulcerative colitis, multiple sclerosis) and for the inhibition of transplanted organs rejection.

INTRODUCTION

A primal cell, stem cells are fundamentally a renovate system in the human body. Stem cells are unspecialized cells with the potential to rise into various different types of cells in the body. They have the capability to proliferate and redevelop themselves. The two main types include embryonic and adult stem cells. In an additional categorization stem cells are divided to totipotent, multipotent and unipotent cells. They are essential to the development, growth, maintenance, and repair of our brains, bones, muscles, nerves, blood, skin, and other organs. Stem cells are found in all of us, from the early on stages of human development to the closing stages of life. When a stem cell divides, each new cell has the potential either to remain a stem cell or, become an additional type of cell with an extra-specialized function, such as a muscle cell, a red blood cell, or a brain cell.

These unspecialized cells are used in treatment of a variety of blood diseases including lymphoblastic leukemia, myeloid leukemia, thalassemia, multiple myeloma and cycle cell anemia. Stem cell based treatments are also valid in case of Parkinson's disease, Amyotrophic lateral sclerosis, Alzheimer, Stroke, Spinal Cord Injury, Multiple Sclerosis, Radiation Induced Intestinal Injury, Inflammatory Bowel Disease, Liver Disease, Duchenne Muscular Dystrophy, Diabetes, Heart Disease, Bone Disease, Renal Disease, Chronic Wounds, Graft-Versus-Host Disease, Sepsis and Respiratory diseases.

“COVID-19” is the sound that surely isn’t forgotten by everybody who lives in the first half of the twenty-first century. COVID-19, as a pandemic, has led many researchers from different biomedical fields to find solutions or treatments to manage the pandemic. However, no standard treatment for this disease has been discovered to date. Almost certainly, preventing the severe acute respiratory infection form of COVID-19 as the most dangerous phase of this disease can be supportive for the treatment and reduction of the death rate. In this regard, Mesenchymal Stem Cells (MSCs)-based immunomodulation treatment has been proposed as a suitable therapeutic approach and more than a few clinical trials have begun. Recently, MSCs according to their immunomodulatory and regenerative properties attract attention in clinical trials. After the intravenous transplantation of MSCs, a major population of cells accumulates in the lung, which they alongside immunomodulatory effect could protect alveolar epithelial cells, retrieve the pulmonary microenvironment, prevent pulmonary fibrosis, and cure lung dysfunction.

A new coronavirus that has a 5% genetic organization with SARS and is a subset of Sarbecovirus [1]. Currently, the virus has been briefly named SARS-CoV-2 virus for additional information and COVID-19, the name was given by the World Health Organization (WHO) to the SARS-CoV-2 virus-associated disease. Coronavirus disease 2019 which known as COVID-19 is the result of one coronavirus infection in the name of SARS-CoV-2. Coronaviruses (CoV) are a large family of viruses that some of them are more known such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV), but some of them are not more known like Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

On March 11, 2020, the WHO characterized the spread of COVID-19 as a pandemic that it has caused unreasonable fear and led to unnecessary suffering and death [12]. To date (29 March 2020), according to the Worldomete site (https://www.worldometers.info/coronavirus/) report more than 199 countries and territories around the world have been affected, with major outbreaks respectively in the USA, Italy, central China, Spain, Germany, and Iran. The mortality rate of COVID-19 has been reported from 0.7% [13] to 15·2% [14] according to different studies in diverse territories and countries. As well, its maximum incubation period has been assumed 2 weeks [15] to 8 weeks [14, 16]. COVID-19 has resulted in that many researchers from different branches of biomedicine were attracted to find a solution or treatment for the management of this pandemic. However, to date haven't been discovered the standard cure for this disease.

Several studies have shown that the first stage of the pathogenesis of this type of virus is the identification of Angiotensin-Converting Enzyme-2 (ACE2) receptor by its spike protein [17] [Figure 1]. For this reason, ACE2-positive cells are infected by this virus [17]. Another study has shown that the cellular protease TMRRSS2 is also required to allow the entry of coronavirus into host cells [18]. It is conceivable that the ACE2 receptor is widely distributed on the surface of human cells, especially Alveolar Type 2 (AT2) and capillary epithelium, and AT2 cells largely express TMPRSS2 [18]. On the other hand, interestingly, bone marrow, lymph nodes, thymus, spleen, and immune cells, such as T and B lymphocytes and macrophages are always negative for ACE2 [19]. These findings suggest that immunoglobulin therapy can help treat patients with the virus infection. Therefore, it should be noted that the capacity of the virus is greatly diminished by the cytokine-induced storm of the virus. The current hallmark of SARS-CoV-2 pathogenesis is the cytokine storm in the

lung. Virally-triggered acute cytokine release of GSCF, IP10, MCP1, MIP1A, IL-2, IL-6, IL-7, and TNF results in pulmonary edema, dysfunction of air-exchange, Acute Respiratory Distress Syndrome (ARDS), and acute cardiac injury, and leading to death [20].

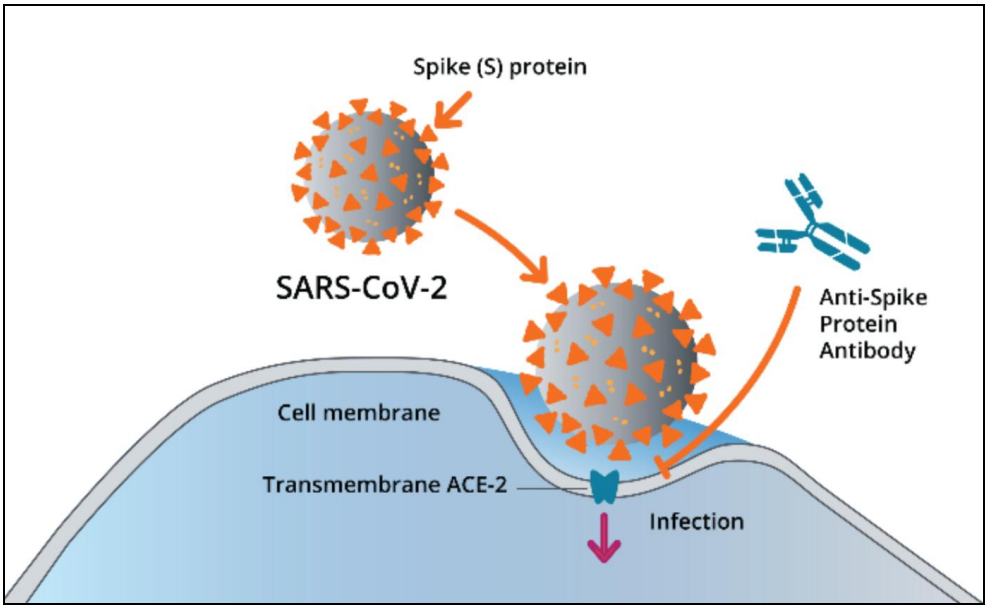

Figure No. 1: Proposed mechanism of action of Corona Virus

Presently, cell-based therapy, and above all, stem cell therapy has proven itself to be one of the most promising therapeutic approaches that provide opportunities to treat several diseases that were considered incurable earlier [21]. MSC therapy is preferred over other therapeutic strategies because they are free of ethical and social issues, they have a high proliferation rate and a low invasive nature. MSCs can be obtained from various sources, including adipose tissues, dental pulp, bone marrow, umbilical cord, menstrual blood, fetal liver, and Bichat's fat pad [22]. MSCs can also be isolated from various adult tissues such as the infrapatellar fat pad, abdominal fat pad, and tissues associated with neonates such as placenta, Wharton's (gelatinous substance providing insulation and protection to the umbilical cord) jelly, cord blood, and amniotic fluid [23]. These stem cells are multipotent (i.e., having several fates). Storage of MSCs can be done so that they can be repetitively used for therapeutic purposes as they expand to volume in a suitable and short period of time [24]. So far, the clinical trials of mesenchymal stem cells have not shown any unfavorable reaction towards the allogeneic MSCs [25]. The efficacy and safety of the MSCs have been documented in many clinical trials very well [26]. To alleviate acute respiratory disease and reverse pulmonary fibrosis in intensive-care SARS-CoV-2-infected patients, three curative properties of MSCs have emerged [Figure 2].

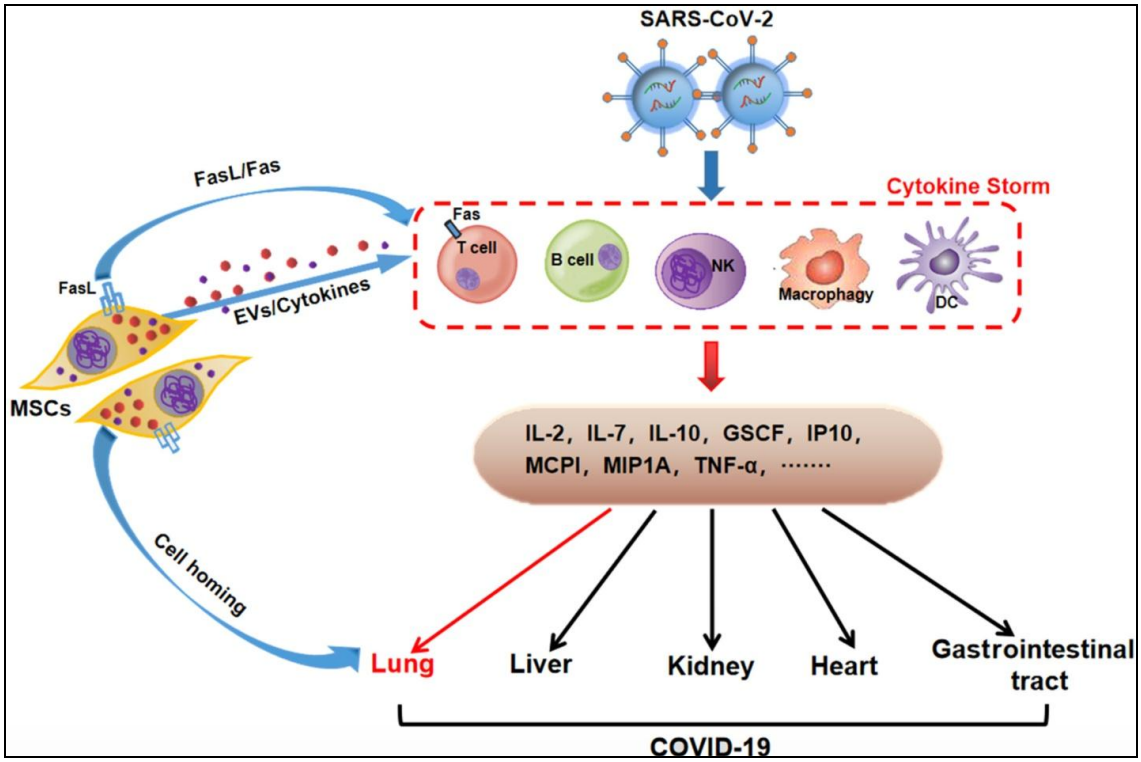

Figure No. 2: Potential mechanism of MSCs in the treatment of severe COVID-19

SARS-CoV-2 (novel coronavirus) and SARS- 2003, both have a similar mechanism of infection, i.e, binding the spike protein on the viral surface to the ACE2 receptors on the host cell surface 27]. Thus all the tissues and organs expressing the ACE2 receptor are susceptible to the SARS-CoV-2 infection. Since the alveolar epithelial cells have a high propensity of ACE2 receptors, they are the most adversely affected during SARS-CoV-2 infection [28]. The devastating cytokine explosion attributed to the SARS-CoV-2infection leads to severe shock, oedema and multiple organ failure. Administering the COVID-19 patients with an infusion of multipotent MSCs can help to combat the COVID-19 as these cells will inhibit the exaggerated immune response and encourage endogenous repair of the lung epithelial cells by improving the microenvironment [29]. The mesenchymal stem cell therapy has nottey shown any adverse side effects on the patient [30]. In this review, we have highlighted all the implications associated with MSC therapy application in case of COVID-19 and strongly place our argument in support of this.

REFERENCES

1. Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, Hu Y, Tao ZW, Tian JH, Pei YY, Yuan ML, Zhang YL, Dai FH, Liu Y, Wang QM, Zheng JJ, Xu L, Holmes EC, Zhang Y-Z. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265–269. doi: 10.1038/s41586-020-2008-3. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
2. Metcalfe, S. M. (2020). Mesenchymal stem cells and management of COVID-19 pneumonia. *Medicine in Drug Discovery*, *100019*. 10.1016/j.medidd.2020.100019.
3. Nidovirales. (2012). In *Virus taxonomy* (pp. 784–794). Elsevier. 10.1016/b978-0-12-384684-6.00066-5.
4. Wong, A. C. P., Li, X., Lau, S. K. P., & Woo, P. C. Y. (2019, February 1). Global epidemiology of bat coronaviruses. *Viruses. MDPI AG.*10.3390/v11020174.
5. Woo, P. C. Y., Wang, M., Lau, S. K. P., Xu, H., Poon, R. W. S., Guo, R., … Yuen, K. -y. (2007). Comparative analysis of twelve genomes of three novel group 2c and group 2d coronaviruses reveals unique group and subgroup features. *Journal of Virology*, *81*(4), 1574–1585. 10.1128/jvi.02182-06.
6. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi Z-L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–273. doi: 10.1038/s41586-020-2012-7. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
7. Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., et al. (2020). A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine.*10.1056/nejmoa2001017.
8. Park, W. B., Kwon, N. J., Choi, S. J., Kang, C. K., Choe, P. G., Kim, J. Y., … Oh, M. D. (2020). Virus isolation from the first patient with SARS-CoV-2 in Korea. *J Korean Med Sci*, *35*(7 PG-84–84), e84–e84. 10.3346/jkms.2020.35.e84.
9. Govorkova EA, Murti G, Meignier B, de Taisne C, Webster RG. African green monkey kidney (Vero) cells provide an alternative host cell system for influenza A and B viruses. Journal of Virology. 1996;70(8):5519–5524. doi: 10.1128/jvi.70.8.5519-5524.1996. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
10. Hoffmann, M., Kleine-Weber, H., Krüger, N., Müller, M., Drosten, C., & Pöhlmann, S. (2020). The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. *bioRxiv*, 2020.01.31.929042. 10.1101/2020.01.31.929042.
11. Li F, Li W, Farzan M, Harrison SC. Structural biology: Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science. 2005;309(5742):1864–1868. doi: 10.1126/science.1116480. [PubMed] [CrossRef] [Google Scholar]
12. WHO. (2020). WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Retrieved March 14, 2020, from https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19%2D%2D-11-march-2020.
13. Ji Y, Ma Z, Peppelenbosch MP, Pan Q. Potential association between COVID-19 mortality and health-care resource availability. The Lancet Global Health. 2020;0(C):30068. doi: 10.1016/S2214-109X(20)30068-1. [CrossRef] [Google Scholar]
14. Baud, D., Qi, X., Nielsen-Saines, K., Musso, D., Pomar, L., & Favre, G. (2020). Real estimates of mortality following COVID-19 infection. *The Lancet Infectious Diseases*, *0*(0). 10.1016/S1473-3099(20)30195-X.
15. (January 2020). Backer, J. A., Klinkenberg, D., & Wallinga, J. (2020). Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20-28. *Euro surveillance: bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin*, *25*(5). 10.2807/1560-7917.ES.2020.25.5.2000062.
16. WHO. (2020). Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19). https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf. Accessed Feb 2020.
17. Rothan, H. A., & Byrareddy, S. N. (2020, February 26). The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *Journal of Autoimmunity. Academic Press*. 10.1016/j.jaut.2020.102433.

18. Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., … Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 10.1016/j.cell.2020.02.052.
19. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. Journal of Pathology. 2004;203(2):631–637. doi: 10.1002/path.1570. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
20. Baruah V, Bose S. Immunoinformatics-aided identification of T cell and B cell epitopes in the surface glycoprotein of 2019-nCoV. Journal of Medical Virology. 2020;92(5):495–500. doi: 10.1002/jmv.25698. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
21. Bhattacharya, M., Sharma, A. R., Patra, P., Ghosh, P., Sharma, G., Patra, B. C., … Chakraborty, C. (2020). Development of epitope-based peptide vaccine against novel coronavirus 2019 (SARS-COV-2): Immunoinformatics approach. *Journal of Medical Virology*, jmv.25736. 10.1002/jmv.25736.
22. Golchin A, Farahany TZ. Biological products: Cellular therapy and FDA approved products. Stem Cell Reviews and Reports. 2019;15(2):1–10. doi: 10.1007/s12015-018-9866-1. [CrossRef] [Google Scholar]
23. Golchin A, Farahany TZ, Khojasteh A, Soleimanifar F, Ardeshirylajimi A. The clinical trials of Mesenchymal stem cell therapy in skin diseases: An update and concise review. Current Stem Cell Research & Therapy. 2018;14(1):22–33. doi: 10.2174/1574888x13666180913123424. [CrossRef] [Google Scholar]
24. Mehta, P., Mcauley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., Manson, J. J., … Collaboration, S. (2020). Correspondence COVID-19: consider cytokine storm syndromes and. The Lancet, 6736(20), 19–20. 10.1016/S0140-6736(20)30628-0.
25. Leng, Z., Zhu, R., Hou, W., Feng, Y., Yang, Y., Han, Q., … Zhao, R. C. (2020). Transplantation of ACE2-Mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging and Disease*, *11*(2), 216. 10.14336/ad.2020.0228.
26. Golchin, A., Shams, F., & Karami, F. (2019). Advancing Mesenchymal stem cell therapy with CRISPR/Cas9 for clinical trial studies. In *Advances in Experimental Medicine and Biology* (pp. 1–12). Springer, New York, NY. 10.1007/5584_2019_459
27. Novello S, Debouche A, Philippe M, Naudet F, Jeanne S. Clinical application of mesenchymal stem cells in periodontal regeneration: A systematic review and meta-analysis. Journal of Periodontal Research. 2020;55(1):1–12. doi: 10.1111/jre.12684. [PubMed] [CrossRef] [Google Scholar]
28. Zhao, K., & Liu, Q. (2016, May 18). The clinical application of mesenchymal stromal cells in hematopoietic stem cell transplantation. *Journal of Hematology and Oncology. BioMed Central Ltd.*10.1186/s13045-016-0276-z.
29. Chen, J., Hu, C., Chen, L., Tang, L., Zhu, Y., Xu, X., et al. (2020). Clinical study of Mesenchymal stem cell treatment for acute respiratory distress syndrome induced by Epidemic Influenza A (H7N9) infection: A hint for COVID-19 treatment. *Engineering.*10.1016/j.eng.2020.02.006.
30. Bing Liang, Junhui Chen, Tao Li, Haiying Wu, Wenjie Yang, Yanjiao Li, J., Li, Congtao Yu, Fangang Nie, Zhaoxia Ma, Mingxi Yang, Panrong Nie, Y. G., & Chuanyun Qian, M. H. (2020). Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord. *China Xiv*, 10.12074/202002.00084.