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Review article

How stem cell therapy can act in the treatment of patients with Covid-19

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Abstract

Introduction: The emergence of a new coronavirus has changed the world and caused one of the biggest global health crises of the past 100 years. The protagonist of the pandemic, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is responsible for the coronavirus disease 2019 (Covid-19), which leads to dysfunctions in a plethora of systems, especially in severe cases. Therefore, researchers and healthcare professionals are making great efforts to develop a therapy that helps the many organs affected by the disease, for which mesenchymal stem cells (MSCs) arise as promising candidates. MSCs can offer benefits at different phases of Covid-19, since they have important anti-inflammatory and tissue repair properties. Objective: This review aims to elucidate how MSCs can contribute in the Covid-19 scenario by considering their properties and mechanisms of action. Methods: A review of the scientific literature was conducted on electronic databases, such as PubMed, Scielo and Web of Science, in the period of 2020-2021. Results: Therapeutic effects of MSCs in preclinical models of respiratory, nervous, renal, and cardiovascular systems were observed. Conclusion: MSCs can be a therapeutic resource for patients with severe Covid-19.

Keywords: SARS-CoV-2; Covid-19; Mesenchymal stem cells; Immunomodulation; Cell therapy.

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Introduction

In 2019, the emergence of a distinct coronavirus revolutionized daily life all over the world. Everything began at the Huanan Seafood Wholesale Market, in Wuhan, China, where many of the staff showed clinical symptoms related to a viral airway disease.[1] This illness has not been restricted to China and has spread to many other countries, including Brazil, in which the first confirmed case occurred in São Paulo on February 26, 2020.[2] The virus was named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) by the International Committee on Taxonomy of Viruses and the disease baptized as Covid-19 (coronavirus disease 2019) by the World Health Organization on January 30, 2020 and assessed as a pandemic on March 11, 2020.[1,3] To this date, more than 180 million cases and over 3.9 million deaths due to Covid-19 have been reported all over the world.[1]

SARS-CoV-2 is classified as a coronavirus belonging to the β-coronavirus genus.[3] Among all the members of the *Coronaviridae* family, it is the seventh virus that is known to be able to infect humans. Its capacity to promote acute respiratory distress syndrome (ARDS) causes the virus to be an important concern, since two other coronaviruses with this syndrome (SARS-CoV and MERS-CoV) have been responsible for epidemics during the last two decades.[4]

SARS-CoV-2

SARS-CoV-2 is a spherical-enveloped virus, with a diameter of 80-120 nm, and a genome composed of a positive-sense single-stranded RNA. The latter is covered by one of the four major structural proteins: the nucleocapsid protein (N). The other three are the

spike glycoprotein (S), the envelope protein (E) and the membrane protein (M), which are contained within the viral envelope.[5] The S is a trimeric glycoprotein that gives the aspect of a crown to the virus surface. It is formed by two subunits: S1, or bulb, and S2, or stalk, and plays an important role in infection.

The gateway for the cell entry of SARS-CoV-2 is the angiotensin-converting enzyme 2 (ACE2), a protein related to the renin-angiotensin system (RAS). This transmembrane receptor can be found in many different sites, including the respiratory, cardiovascular, urinary and digestive organs.[6] The S protein mediates viral entry, and the protein is processed by a serine protease named TMPRSS2, another enzyme that has been shown to be crucial to the infection process. The cleavage of the S protein exposes the S1 subunit, which contains the receptor-binding domain (RBD) that is responsible for interacting with ACE2. Meanwhile, the S2 subunit allows the fusion of the viral and host cell membranes. Replication and translation steps start as soon as the viral RNA reaches cytosol, producing new virions that are able to infect other cells.[5]

The human airway is the main entry point for SARS-CoV-2. Once inside the lungs, the virus primarily infects type-II pneumocytes and alveolar macrophages, while reaching other organs through the bloodstream after some viral cycles.[7] The respiratory tract is not only the entry point but also the major exit point of the virus. Droplets and aerosol exhaled by infected patients are the most important means of transmission, followed by direct contact with contaminated fomites.[8]

Covid-19

Since its outbreak, researchers and healthcare professionals have been thoroughly studying Covid-19, which appears to be a complex disease as new data arise over time. Five different clinical conditions of Covid-19 have been observed: asymptomatic, mild, moderate, severe and critical cases. Most patients manifest mild to moderate symptoms, which include fever, dry cough, sore throat, loss of smell and taste, fatigue and shortness of breath. In severe and critical cases, these symptoms rapidly evolve to pneumonia and hypoxemia (low oxygen saturation), and can develop into ARDS and multiple organ dysfunction as a result of an impaired immune response, which can be fatal.[9] Comorbidities, such as cardiovascular diseases and diabetes, enhance the risk of the worst outcomes.[10]

Cell-based therapies

Currently, vaccines are considered as one of the few promises for better days. Since February of 2021, some of them have already been approved and applied worldwide, while others are undergoing clinical trials and approval.[11] However, vaccination campaigns are slow and mortality rates remain high, either due to the risk factor associated with age or the appearance of new variants of the virus in many different countries. Therefore, new therapies, such as cell-based therapies, are essential to provide an adjuvant treatment for Covid-19. Over the years, stem cells have been widely used as a form of therapy for several acute and chronic diseases in experimental models and clinical trials. These cells show promise due to their ability to promote tissue parenchyma regeneration and repair, whether they are embryonic stem cells (ESCs), induced pluripotency stem cells (iPSCs), bone marrow mononuclear cells (BMMC) or mesenchymal stem cells (MSCs).[12] ESCs and iPSCs have therapeutic potential because of their capacity to differentiate into various cell lines, giving hope to patients suffering from diabetes, Parkinson's disease, cardiovascular disease and liver disease. Currently, iPSCs have been used to generate organoids of the liver, stomach, kidney, nervous system, thyroid glands and lungs, whose potential for expansion at an industrial level for translational use is helpful. Organoid applications aim to modulate responses from patient-specific drugs in tumorigenesis or infectious diseases.[13] Nevertheless, taking into account ethical, legal and biological limitations, the use of adult stem cells, such as MSCs, is more favorable in clinical practice.[14]

Mesenchymal stem cells

MSCs are a promising tool in cell therapy for treating many incurable diseases, due to their multipotent differentiation, self-renewal, immunoregulation, tissue regeneration effects and capacity for inflammation reduction. In addition, MSCs have the ability to differentiate into three types of cells: osteoblasts, chondroblasts and adipocytes.[15] Easily obtainable, MSCs can be found in most vascularized tissues, such as bone marrow, adipose tissues, umbilical cords, fetal livers, fetal lungs, mobilized peripheral blood, dental pulp, placentas and even menstrual blood, but can also be generated from embryonic stem cells.[16] These cells are considered safe, even in an allogeneic

environment, and avoid immune responses due to their low expression of MHC-I and MHC-II.

MSCs can act in many different ways within the body, using their immunomodulatory, paracrine properties, differentiation and antimicrobial potential.[16] They can provide an ideal environment for hematopoietic stem cells in the bone marrow by releasing some extracellular matrix proteins, such as laminin and fibronectin.[15]

The therapeutic effects of MSCs are mainly expressed through growth and survival factors by paracrine signaling, such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), and insulin-like growth factor-1 (IGF-1). These promote angiogenesis, cell survival and cell proliferation, thereby reducing inflammation, apoptosis and fibrosis of injured tissues. Furthermore, MSCs can directly inhibit the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), by immunosuppressive responses in innate and adaptive immune systems. For example, MSCs can interact with Th2 lymphocytes and attenuate NK cell responses by inducing the transition of M1 macrophages to M2 anti-inflammatory phenotypes, thereby increasing the secretion of anti-inflammatory cytokines, including IL-10, IL-12p40.[15]

Recently, it has been discovered that the immunomodulatory action of MSCs is activated only if exposed to a sufficiently high level of pro-inflammatory cytokines and nitric oxide, such as the cytokine storm in Covid-19 infection. Therefore, MSCs have great antimicrobial potential, whether acting through immunomodulation or directly through the expression of antimicrobial peptides (AMPs).[16] MSCs can also transfer healthy mitochondria to other cells through tunneling nanotubes, thereby improving the anti-inflammatory response.[15]

Extracellular vesicles (EVs) are another mechanism of action of MSCs, by acting as mediators for intercellular communication, which involves carrying biological messengers into injured sites.[17] EVs comprise microvesicles and exosomes, which contain transcription factors, growth factors, cytokines, mRNAs, and microRNAs (miRNAs), and are responsible for homeostasis, coagulation, angiogenesis, inflammation and antiapoptotic effects. EVs are nanovesicles measuring 30–150 nm that originate from the direct budding of the cell membrane or via endosomal secretion. They are composed of cytosolic contents and a lipid bilayer similar to their mother cell and, therefore, can mimic cell interactions between the source and the target.[18]

Moreover, MSCs and MSC-EVs are considered potential instruments in therapy due to acting simultaneously in crucial mechanisms of tissue damage, mainly through tissue remodeling, by modulating inflammatory cells and signals, thus enhancing tissue survival, and favoring angiogenesis, while presenting a low risk of immunogenicity and tumorigenicity.[18] Thus, MSCs are suitable candidates for cell therapy in Covid-19.

Pathophisiology of Covid-19

The main site of SARS-CoV-2 infection is the lungs, more specifically the alveoli, through the invasion of type 2 pneumocytes, macrophages and ACE2-receptor positive cells.[7] The lungs of Covid-19 patients develop diffuse alveolar damage, intra-alveolar fibrosis, bronchopneumonia, and even necrotizing bronchiolitis in severe cases.[19] The interplay between SARS-CoV-2 infected cells and resident immune cells, such as macrophages and dendritic cells, triggers a cascade of inflammatory events, producing cytokines and chemokines while stimulating the recruitment of inflammatory cells.[20] As the epithelial lining is damaged and inflammatory infiltration takes place, exudate builds up and occupies the air space within the lungs. This process also contributes to the thickening of the alveolar wall and interstitial fibrosis, culminating in the formation of a hyaline membrane that hinders air exchange.

Covid-19 pathogenesis also affects the circulatory component of the lungs. SARS-CoV-2 can directly infect endothelial cells, since these cells express ACE2 receptors.[10] Covid-19 causes more thrombotic disorders and endothelial damage than other respiratory viruses, such as SARS-CoV, MERS-CoV, and influenza.[21] These thrombotic microvascular lesions are mediated by an intense activation and deposition of complement system proteins, such as C5b-9, C4d, and MASP2, within the pulmonary septum microvasculature.[20] Therefore, disturbances in circulation and air exchange result in lower O2 distribution throughout the body.

Notably, SARS-CoV-2 triggers the release of pro-inflammatory cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL-6). GM-CSF stimulates inflammatory monocytes and macrophages to produce more IL-6 and TNF-α. With the progression of Covid-19 pathogenesis, infected cells and nearby cells are exposed to

intracellular components not usually found outside the cell, which causes pyroptosis.[22] This type of cell death leads to inflammasome signaling, starting a cascade of IL-1 and the release of other inflammatory factors. This further increases the process of inflammation, forming a vicious cycle of continuous inflammatory damage.

If the body is unable to limit the damage and subsequent inflammation, the condition evolves into a cytokine storm, characterized by increased levels of circulating inflammatory cytokines (IL-6, IL-8, TNF-α, monocyte chemoattractant protein-1 (MCP1), and RANTES) and ultimately damages other organs.[23]

Since Covid-19 treatment is still deficient, novel therapies that might help bed-ridden patients are in great need. In this regard, the capacity of MSCs to regulate the immune response or improve tissue regeneration may be used to control the principal components of Covid-19 pathology in severe cases: exacerbated inflammation with cytokine storm and severe lung damage.

Possible therapeutic targets and mechanisms of mesenchymal stem cells in Covid-19

Therapies using MSC are a potentially promising alternative strategy for the treatment of Covid-19, since when it comes to lung diseases, MSCs can modulate the activation and effector function of immune cells by suppressing infiltrated cells and reducing edemas.[24] Repair is provided by the property that MSCs have to incorporate into traumatized tissue and secrete growth factors, RNAs, microRNAs by paracrine/endocrine mechanisms, forming a beneficial microenvironment that aids in tissue repair.[25] However, the available records on MSC therapy for Covid-19 are still limited.

The therapeutic potential of MSCs has been demonstrated in other viral respiratory diseases. In H9N2 avian influenza-infected mice, MSC therapy reduced acute lung injury and inflammation. MSCs were capable of increasing the survival rate, decreasing lung edemas and histological injury and improving gas exchange, as well as reducing alveolar pro-inflammatory chemokines and cytokines. In a swine model of H1N1, the extracellular vesicles of MSCs reduced lung injury by reducing the production of pro-inflammatory cytokines, viral shedding and replication while also decreasing virus-induced apoptosis of alveoli epithelial cells.[26]

However, H1N1-infected mice administered with MSCs, although showing a modest reduction of viral load and lower thrombocytosis, did not display any improvements in survival, histopathology, inflammatory profile resolution or prevention.[27] Since the virus-induced ARDS model is not yet fully established, the therapeutic effect of MSCs is still under question in certain viral scenarios.

Nonetheless, MSCs have demonstrated many possible mechanisms for improving the resolution of ARDS through their anti-inflammatory and antiapoptotic effects on host cells. They reduce the permeability of the lung alveolar epithelium, increase the clearance of alveolar fluid and enhance host mononuclear cell phagocytic activity.[28] MSCs have demonstrated an ability to restore alveolar fluid clearance in *ex vivo* perfused human lungs. They have also improved epithelial integrity and regulation by transferring healthy mitochondria to epithelial cells, reducing oxidative damage and apoptosis, thus increasing survival in mice.[29]

Direct mitochondrial transfer can also modulate immune response by favoring Treg cell phenotype, which restricts inflammatory responses or the production of macrophages, thereby increasing phagocytosis.[30]

MSCs can modulate inflammation and protect the endothelial tissue of the lung.[31] MSCs secrete VEGF, which promotes angiogenesis, and HGF, which stabilizes the endothelial barrier function by restoring pulmonary capillary permeability. This proangiogenic signaling inhibits pulmonary vascular endothelial cell apoptosis.[32] In *ex vivo* human lungs, MSCs reduced endothelial permeability and protected against inflammatory disruption of barrier function, thereby restoring alveolar fluid clearance in the LPS-ARDS model.[31]

Thus, we can speculate that MSC therapy could modulate inflammation, by regulating the permeability of both endothelial and epithelial barriers during Covid-19 and preventing dysfunction.

Covid-19 multi-organ damage and potential mesenchymal stem cells therapy

Besides the classical and expected symptoms in virus-induced pneumonia, such as hypoxemia and ARDS, Covid-19 has proven to be more than a respiratory disease, causing symptoms in a variety of organs. If the cytokine storm persists, it may progress to mul-

tiple organ dysfunction syndrome,[9] affecting renal, cardiovascular, nervous, and gastrointestinal systems, which have high expression of ACE2 receptors.[6]

Severe Covid-19 seems to trigger myocarditis-like disorders, causing chest pressure and displaying increased protein levels of cardiac troponin, myoglobin, creatine kinase and NT-proBNP. Myocardial injury occurs in ~25% of Covid-19 hospitalized patients and is associated with a greater need for mechanical ventilator support and higher hospital mortality.[33] Therapeutic effects of MSCs in cardiac tissue have been reported.[31] In a model of mouse myocarditis by Coxsackievirus B3, MSCs exhibited a cardioprotective role in the recovery of myocardial contractility and fibrosis by the activation of resident cardiac stem cells.[34]

Covid-19 can also promote acute renal injury.[4] SARS-CoV-2 can infect renal cells, since viral particles are found near ACE-2 expressing cells, such as renal tubular epithelium and glomerular capillaries.[4,35] MSCs have been shown to improve renal injury by reducing tubulointerstitial fibrosis and TGF-β, which plays a key role in fibrogenesis.[36] In addition, MSCs also have the ability to promote anti-inflammatory effects at long distances. Even though intravenously infused MSCs are retained in the lungs, evidence has shown that a combination of exosomes with soluble factors secreted by MSCs contributes to anti-inflammatory response and the regeneration of renal tissues.

Moreover, MSCs can be beneficial even in indirect Covid-19 injuries. In a ventilator-induced lung injury, MSCs or even MSC-conditioned media decreased bronchoalveolar liquid concentrations of cytokines and inflammatory cells.[37]

Therefore, Covid-19 can generate an immune system overreaction causing a cytokine storm followed by edemas, inefficient gas exchange, ARDS, cardiac and renal impairments and possibly allowing secondary infections. Since the resolution of Covid-19 is mainly dependent on the function of patients' immune systems, avoiding cytokine overproduction is decisive in the recovery of patients with Covid-19. MSCs can play a crucial role, by minimizing the symptoms of Covid-19 and giving a chance for the patient's immune system to react against the virus and promote pulmonary regeneration.

Future challenges and perspectives

Since the outbreak of Covid-19 in early 2020, numerous studies have been made with the aim of developing new therapeutic interventions to control the disease and its possible impacts on the population. MSCs are a major cornerstone in the advancement of cell therapy, presenting positive results in multiple disease clinical trials, such as virus-induced ARDS.[34] The applicability of MSCs is not restricted to utilizing only the cells themselves, but also extends to MSC-derived products, such as the secretome and EVs, opening one more possibility in the future.[17,18] Their therapeutic action is probably attributable to their broad range of anti-inflammatory and regenerative effects, which help to heal damaged tissue.[38] Most importantly, MSCs do not express ACE2 and TMPRSS2 since they are not conducive to SARS-CoV-2 infection, which supports the safety of MSCs as a plausible therapy.[39]

It is also relevant to consider aspects that will reflect on the effectiveness of MSC therapy for Covid-19. For example, the donor tissue source of MSCs, which constitutes the MSCs' microenvironment and modulates their behavior and capacity, can greatly affect their therapeutic potential. Metabolic diseases, such as obesity and *diabetes mellitus*, also have an influence on the behavior of MSCs and compromise their therapeutic efficacy.[40] Therefore, exploratory studies that seek to maintain the phenotype and potential of MSCs are necessary for clinical practice, to understand better how the clinical conditions of MSC donors influence the viability and therapeutic capacity of this treatment.

Moreover, the timing and dosage of MSCs for Covid-19 are still in question, since defining the optimal stage of Covid-19 at which the cells present the most benefit to the patient must still be clarified. Also, with the emergence of long Covid patients who suffer from Covid-related symptoms over an extended period of time even after the resolution of the acute infection, interest in the antifibrotic and regenerative potential of MSCs will increase. Standardized protocols are needed to further investigate and validate this therapeutic approach in order to enhance the applicability of MSCs in the treatment of Covid-19 disease.

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References

1. WHO. Coronavirus Disease (Covid-19) Situation Reports. Situat Reports WHO Accessed June 30, 2021; 2021
2. Candido DDS, Watts A, Abade L, et al. Routes for Covid-19 importation in Brazil. J Travel Med. 2020 May;27(3). doi: 10.1093/jtm/taaa042
3. Gorbalenya AE, Baker SC, Baric RS, et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020;5(4):536–44. doi: 10.1038/s41564-020-0695-z
4. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265–9. doi: 10.1038/s41586-020-2008-3
5. Jin Y, Yang H, Ji W, et al. Virology, epidemiology, pathogenesis, and control of Covid-19. Viruses. 2020;12(4):1–17. doi: 10.3390/v12040372
6. Li M-YY, Li L, Zhang Y, et al. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty. 2020 Apr;9(1):45. doi: 10.1186/s40249-020-00662-x
7. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in Covid-19. Vol. 75, Allergy: European Journal of Allergy and Clinical Immunology. Blackwell Publishing Ltd; 2020. p. 1564–81. doi: 10.1111/all.14364
8. Meyerowitz EA, Richterman A, Gandhi RT, et al. Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors. Ann Intern Med. 2021;174(1):69–79. doi: 10.7326/M20-5008
9. Robba C, Battaglini D, Pelosi P, et al. Multiple organ dysfunction in SARS-CoV-2: MODS-CoV-2. Expert Rev Respir Med. 2020 Sep;14(9):865–8. doi: 10.1080/17476348.2020.1778470
10. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91–5. doi: 10.1016/j.ijid.2020.03.017
11. Li Y, Tenchov R, Smoot J, et al. A Comprehensive Review of the Global Efforts on Covid-19 Vaccine Development. ACS Cent Sci. 2021 Apr;7(4):512–33. doi: 10.1021/acscentsci.1c00120
12. Zakrzewski W, Dobrzyński M, Szymonowicz M, et al. Stem cells: past, present, and future. Stem Cell Res Ther. 2019;10(1):68. doi: 10.1186/s13287-019-1165-5
13. Eguizabal C, Aran B, Chuva de Sousa Lopes SM, et al. Two decades of embryonic stem cells: a historical overview. Hum Reprod Open. 2019 Jan;2019(1). doi: 10.1093/hropen/hoy024
14. Esquivel D, Mishra R, Soni P, et al. Stem Cells Therapy as a Possible Therapeutic Option in Treating Covid-19 Patients. Stem Cell Rev Reports. 2021;17(1):144–52. doi: 10.1007/s12015-020-10017-6
15. Dabrowska S, Andrzejewska A, Janowski M, et al. Immunomodulatory and Regenerative Effects of Mesenchymal Stem Cells and Extracellular Vesicles: Therapeutic Outlook for Inflammatory and Degenerative Diseases. Front Immunol. 2021;11:3809. doi: 10.3389/fimmu.2020.591065
16. Verma YK, Verma R, Tyagi N, et al. Covid-19 and its Therapeutics: Special Emphasis on Mesenchymal Stem Cells Based Therapy. Stem cell Rev reports. 2021 Feb;17(1):113–31. doi: 10.1007/s12015-020-10037-2
17. Rezakhani L, Kelishadrokhi AF, Soleimanizadeh A, et al. Mesenchymal stem cell (MSC)-derived exosomes as a cell-free therapy for patients Infected with Covid-19: Real opportunities and range of promises. Chem Phys Lipids. 2021 Jan;234:105009. doi: 10.1016/j.chemphyslip.2020.105009
18. Keshtkar S, Azarpira N, Ghahremani MH. Mesenchymal stem cell-derived extracellular vesicles: novel frontiers in regenerative medicine. Stem Cell Res Ther. 2018;9(1):63. doi: 10.1186/s13287-018-0791-7
19. Vasquez-Bonilla WO, Orozco R, Argueta V, et al. A review of the main histopathological findings in coronavirus disease 2019. Hum Pathol. 2020;105:74-83. doi: 10.1016/j.humpath.2020.07.023
20. Schaefer I-M, Padera RF, Solomon IH, et al. In situ detection of SARS-CoV-2 in lungs and airways of patients with Covid-19. Mod Pathol. 2020;33(11):2104-14. doi: 10.1038/s41379-020-0595-z
21. Bikdeli B, Madhavan M V., Jimenez D, et al. Covid-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. Vol. 75, Journal of the American College of Cardiology. Elsevier USA; 2020. p. 2950-73. doi: 10.1016/j.jacc.2020.04.031
22. Ferreira AC, Soares VC, de Azevedo-Quintanilha IG, et al. SARS-CoV-2 engages inflammasome and pyroptosis in human primary monocytes. Cell Death Discov. 2021;7(1). doi: 10.1038/s41420-021-00477-1
23. Hu B, Huang S, Yin L. The cytokine storm and Covid-19. J Med Virol. 2021 Jan;93(1):250–6. doi: 10.1002/jmv.26232
24. Liu S, Peng D, Qiu H, et al. Mesenchymal stem cells as a potential therapy for Covid-19. Stem Cell Res Ther. 2020;11(1):169. doi: 10.1186/s13287-020-01678-8
25. Lindoso RS, Collino F, Bruno S, et al. Extracellular Vesicles Released from Mesenchymal Stromal Cells Modulate miRNA in Renal Tubular Cells and Inhibit ATP Depletion Injury. Stem Cells Dev. 2014 Mar;23(15):1809–19. doi: 10.1089/scd.2013.0618
26. Khatri M, Richardson LA, Meulia T. Mesenchymal stem cell-derived extracellular vesicles attenuate influenza virus-induced acute lung injury in a pig model. Stem Cell Res Ther. 2018;9(1):17. doi: 10.1186/s13287-018-0774-8
27. Laffey JG, Matthay MA. Cell-based therapy for acute respiratory distress syndrome: Biology and potential therapeutic value. Vol. 196, American Journal of Respiratory and Critical Care Medicine. American Thoracic Society; 2017. p. 266–73. doi: 10.1164/rccm.201701-0107CP
28. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe Covid-19 infection: A report of five cases. Transl Res. 2020;220:1–13. doi: 10.1016/j.trsl.2020.04.007
29. Islam MN, Das SR, Emin MT, et al. Mitochondrial transfer from bone-marrow–derived stromal cells to pulmonary alveoli protects against acute lung injury. Nat Med. 2012;18(5):759–65. doi: 10.1038/nm.2736
30. Court AC, Le-Gatt A, Luz-Crawford P, et al. Mitochondrial transfer from MSCs to T cells induces Treg differentiation and restricts inflammatory response. EMBO Rep. 2020 Feb;21(2). doi: 10.15252/embr.201948052
31. Németh K, Leelahavanichkul A, Yuen PST, et al. Bone marrow stromal cells attenuate sepsis via prostaglandin E2–dependent reprogramming of host macrophages to increase their interleukin-10 production. Nat Med. 2009;15(1):42–9. doi: 10.1038/nm.1905
32. Wang J, Jiang M, Chen X, et al. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 Covid-19 patients in China and emerging pathogenesis

and therapy concepts. J Leukoc Biol. 2020 Jul;108(1):17–41. doi: 10.1002/JLB.3COVR0520-272R

33. Giustino G, Pinney SP, Lala A, et al. Coronavirus and Cardiovascular Disease, Myocardial Injury, and Arrhythmia: JACC Focus Seminar. J Am Coll Cardiol. 2020;76(17):2011–23. doi: 10.1016/j.jacc.2020.08.059
34. Walter J, Ware LB, Matthay MA. Mesenchymal stem cells: Mechanisms of potential therapeutic benefit in ARDS and sepsis. Vol. 2, The Lancet Respiratory Medicine. Lancet Publishing Group; 2014. p. 1016–26. doi: 10.1016/S2213-2600(14)70217-6
35. Allison SJ. SARS-CoV-2 infection of kidney organoids prevented with soluble human ACE2. Nat Rev Nephrol. 2020;16(6):316. doi: 10.1038/s41581-020-0291-8
36. Lira R, Oliveira M, Martins M, et al. Transplantation of bone marrow-derived MSCs improves renal function and Na++K+-ATPase activity in rats with renovascular hypertension. Cell Tissue Res. 2017 Aug;369(2):287–301. doi: 10.1007/s00441-017-2602-3
37. Curley GF, Ansari B, Hayes M, et al. Effects of Intratracheal Mesenchymal Stromal Cell Therapy during Recovery and Resolution after Ventilator-induced Lung Injury. Anesthesiology. 2013 Apr;118(4):924–32. doi: 10.1097/ALN.0b013e318287ba08
38. Pittenger MF, Discher DE, Péault BM, et al. Mesenchymal stem cell perspective: cell biology to clinical progress. npj Regen Med. 2019;4(1):22. doi: 10.1038/s41536-019-0083-6
39. Avanzini MA, Mura M, Percivalle E, et al. Human mesenchymal stromal cells do not express ACE2 and TMPRSS2 and are not permissive to SARS-CoV-2 infection. Stem Cells Transl Med. 2021 Apr;10(4):636-42. doi: 10.1002/sctm.20-0385
40. de Oliveira GP, Cortez E, Araujo GJ, et al. Impaired mitochondrial function and reduced viability in bone marrow cells of obese mice. Cell Tissue Res. 2014 Jul;357(1):185–94. doi: 10.1007/s00441-014-1857-1