Scientific Research Publishing

Stem Cell Discovery, 2022, 12, 1-27
https://www.scirp.org/journal/scd
ISSN Online: 2161-6787
ISSN Print: 2161-6760

Stem Cells: A Promising Therapeutic Target for COVID-19

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How to cite this paper: Hardin, L.T. and Xiao, N. (2022) Stem Cells: A Promising Therapeutic Target for COVID-19. *Stem Cell Discovery*, **12**, 1-27.
https://doi.org/10.4236/scd.2022.121001

Received: January 3, 2022
Accepted: January 25, 2022
Published: January 28, 2022

Abstract

A large variety of therapeutic products have been developed as vaccines or treatments of COVID-19 infection. Meanwhile SARS-CoV-2 continues to mutate and spread. The severe COVID-19 patients have limited treatment options. Therefore, mesenchymal stem cells (MSCs) are proposed as another therapeutic target. They are known for their regenerative and immunomodulatory properties. They showed potent efficacy and safety abilities for the treatment of critical COVID-19 patients and intriguing benefits in reducing lungs damage, mortality, and cytokine storm in several clinical studies. Another promising treatment option is the use of dental pulp stem cells (DPSCs) to combat SARS-CoV-2, despite the fact that detailed therapeutic strategies and mechanisms are still lacking. In this review we shed light on the immune response against COVID-19 infection and the relevant knowledge considering the role of MSCs in innate and adaptive immune responses to better understand the immunophysiological mechanisms of MSCs treatment. Lastly, we summarize the latest progress in clinical and research studies suggesting potential MSCs/DPSCs as therapeutic targets in battling COVID-19.

Keywords

ACE2, Clinical Use, Exosomes, Immunotherapy, Mesenchymal Cells, SARS-CoV-2

1. Introduction

Although the COVID-19 pandemic began over two years ago and the pathological mechanisms of SARS-CoV-2 have sufficiently been revealed, there is no current effective treatment [1] [2]. The virus provokes cytokine storm [3], in which hyperinflammation and severe multiorgan failure were observed through excessive cytokine release from uncontrolled immune activation [4]. Stem cells therapy is one of the numerous therapeutic avenues used to save people's lives espe-

cially in severe COVID-19 cases [5]. MSCs are stromal cells that originated from different tissues such as bone marrow, fat, dental tissue, umbilical cord, placenta, and many other sources [6] [7] [8] [9]. MSCs possess immunomodulatory capabilities as well as their endowed regenerative ability and multipotency [8] [10]. After infecting the host cells, SARS-CoV-2 showed ability to overcome the host immune system [11]. MSC therapies were showed to be a fruitful avenue to treat COVID-19 infection [3] [12] [13]. Hence, several MSCs therapy clinical studies (clinical trials, patient case reports) have been reported. An impressing decrease of inflammatory cytokines was observed few days after administration of the MSCs, in addition to a decrease of lung damage and time to recovery [2] [3]. Moreover, a great survival rate and MSCs tolerance were reported [14] [15] [16] [17] [18]. DPSCs are MSCs isolated from the dental pulps. They share many similarities with bone marrow MSCs and present many unique proprieties such as the easy isolation, great proliferation and differentiation potentials, and immunomodulatory activity [19] [20] [21]. In addition, they are characterized by a low immunogenicity. All these properties make them great candidates for the treatment of COVID-19. DPSCs have been shown to be efficient as a potential therapy for severe COVID-19 and they have shown a great curative potential despite the lack of a full understanding of the mechanisms [22] [23]. DPSCs hold promising immunomodulatory potential that might enhance their medical use in infectious diseases and inflammation [24].

Standardizing MSC use and MSC derivatives protocols are fundamental [2]. In order to determine the cell-therapy products, cells, tissues, or products derived from cells and tissues are categorized as pharmaceutical methods by the US Food and Drug Administration (US FDA) [2] [25]. The umbilical cord blood is the sole stem cell product approved for use in patients who have blood production problems [2] [26].

Immuno-regulators agents seemed to play a key role in fighting COVID-19 infection. With more reports and ongoing research revealing the possible viral pathological pathways and virus-host interactions, mechanism of therapeutic strategies could be better elucidated, and alternative treatments are being investigated. Some studies suggest that the immunomodulatory potential of MSCs is particularly paracrine and it results from MSC-derived exosome which could be secreted as extracellular vesicles (EVs) through paracrine pathway [27] [28]. The exosomes contain a variety of cargos, including messenger ribonucleic acids (mRNAs), DNA, lipids, growth factors, carbohydrates, and miRNAs [29] [30] [31].

This paper discusses the plausible MSCs as well as DPSCs immuno-modulatory potentials to suppress COVID-19 infection. Also, we particularly review the recent progress in MSC therapy in clinical and research studies.

2. Immune Response against COVID-19

When SARS-CoV-2 invades the host cell, the immune system tries to eliminate

the virus through the innate and acquired immunity [32] (**Figure 1**).

2.1. Innate Immune Response

SARS-CoV-2 cell entry is insured by many cellular players such as ACE2, TMPRSS2, integrins, neuropilins 1, DC/L-SIGN, and C-type lectins mediated endocytosis [33] [34] [35] [36]. It is reported that viral mRNA is recognized by Toll-like receptor (TLR) which triggers transcriptional responses and cytoplasmic changes that generate the induction of the Nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome [32]. NLRP3 is an intracellular pattern recognition receptor (PRR) sensor that recognizes a large variety of microbial motifs, intracellular danger signals and extracellular stressors [37]. Activated NLRP3 then recruits adaptor and effector proteins to form inflammasome and provokes caspase 1-mediated secretion of the pro-inflammatory cytokines IL-1β and IL-18, and gasdermin [37] [38] [39], which further induces pyroptosis [40], inflammation [41] and coagulopathy [42].

The virus hijacks the immunity actors and triggers a cytokine storm [43] [44] [45] [46] [47]. These chemokines are chemotactic cytokines that play a major role in controlling the migration, the positioning of immune cells in tissues, and the selective recruitment of innate immune effectors [48]. Stimulated macrophages release tumor necrosis factor α (TNF-α) and interleukin-1β (IL-1β) which activates the innate immune system and triggers the acute inflammatory response immediately following infection. Interferon-γ (IFN-γ) is

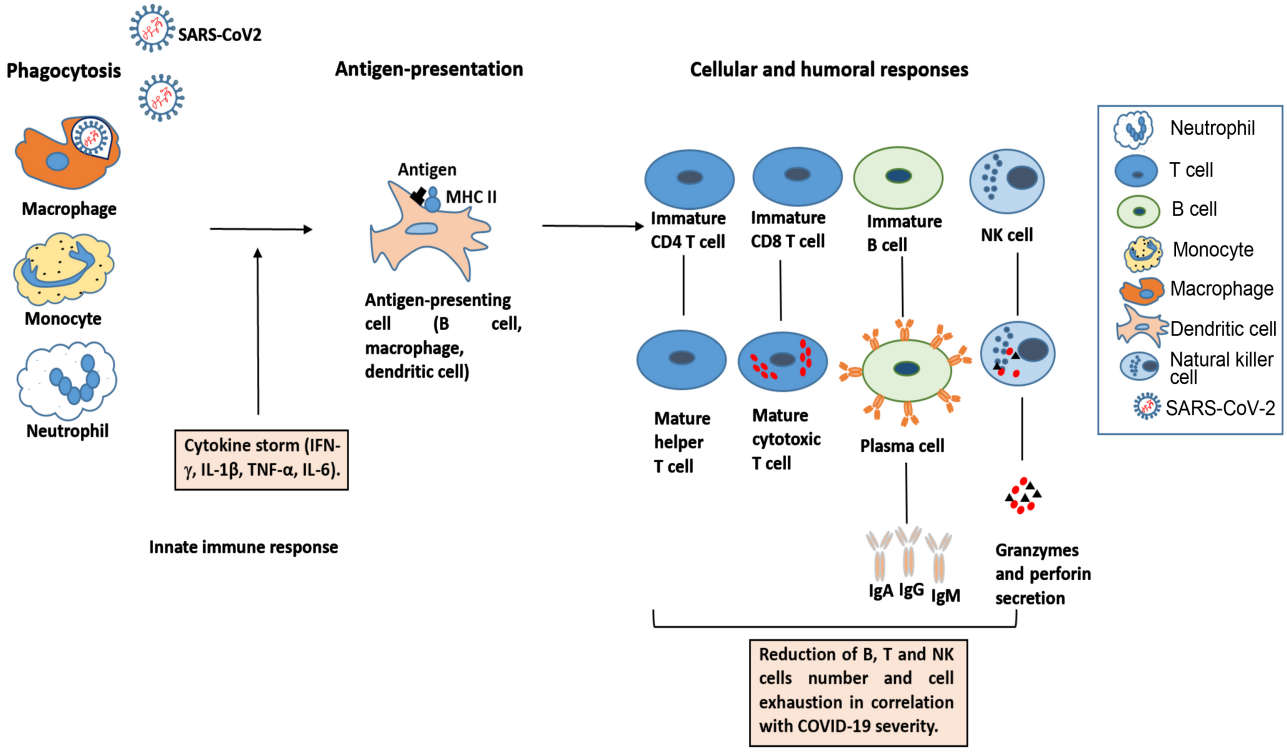

Figure 1. Innate and adaptative immune response of MSCs to COVID-19.

essentially secreted by activated T cells and natural killer (NK) cells, and its principal roles are the stimulation of the macrophage population, the achievement of antigen presentation and the mobilization of the innate immune system and the antimicrobial immunity [49]. A high plasma level of interferon IFN-γ was noticed in COVID-19 patients [50]. Also, a significant increase in plasma levels of the inflammatory interleukins (IL-1β, IL-8, and TNF-α) and the anti-inflammatory interleukins (IL-6, IL-10) was reported [51] [52]. Besides, the monocyte chemoattractant peptide (MCP)-1, which is a key player in monocytes/macrophages recruitment [53], was found with high concentration in COVID-19 patients [54]. Similarly, granulocytes colony stimulating factor (G-CSF), MIP)-1A and MIP-1B, and MIP were found to be abundant in plasma of COVID-19 which stimulates the "emergency production" of neutrophils that occurs in response to acute injury or infection [52].

SARS-CoV-2 showed to trigger cell pyroptosis, which is a programmed cell death with pro-inflammatory cytokines [55]. Indeed, the high secretion of cytokines recruit different immune cells to the site needed [56], which partially reveals the lymphopenia especially in severe cases of COVID19 [57]. It appears that SARS-CoV-2 acts by differentially suppressing some cells and activating other cells, lymphocytes were found to decrease in opposite neutrophils showed to increase [52] [58].

2.2. Adaptive Immunity

Upon stimulation by the pathogen, T helper 1 (Th1) and NK cells secrete IFN-γ, which induces macrophages, activates antigen processing, and coordinates both innate and adaptive immune response [49]. The number of $CD8^+$ T and NK cells was found to decrease but the cells were particularly induced. Cell lytic granules (perforin and granzyme) were greatly detected in some immune cells [56], which can impair the viral infection but also disrupt the cellular mechanisms [59].

$CD4^+$ T and B cells numbers were not correlated to COVID-19 severity [60], but in the study of Wang *et al.* the B cells number remarkably decreased in severe and critical cases [61]. The study of Bobcakova *et al.* reported that memory B cell frequency was significantly reduced in asymptomatic and critical cases [62]. COVID-19 patients showed a low count of lymphocytes especially for patients with severe disease [63], and the counts of T cells, NK cells, T helper cells, cytotoxic T cells (also known as $CD8^+$ cells), and Treg cells also decreased, which yield a reduction of their capabilities to battle the virus infection [64] [65].

SARS-CoV-2 humoral immune response is mediated by antibodies that are targeting viral surface glycoproteins, mainly S and N. As the coronavirus S glycoprotein is surface-exposed and insures entry into host cells, it represent essentially the most targetable protein the neutralizing antibodies [66]. The study of Sterlin *et al.* showed that IgA antibodies were detected earlier than other antibodies in COVID-19 disease [67]. Moreover, serum IgA showed to be more efficient in neutralizing the virus than IgG. IgM and IgA antibodies showed to be detectable early during the first week of symptoms appearance, but IgG showed

to be identifiable at least two weeks from the appearance of symptoms. IgM seropositivity level was reported to decline after 4 weeks, whereas IgG and IgA seropositivity persisted at detectable level for more than eight weeks [68].

Determining IgA and IgG subclasses helps to understand the infection mechanisms. The study of Dogan *et al.*, reported that the IgG1 subclass was the most dominant in COVID-19 cases, but other subclasses were detectable such as IgA and IgG2-4 at lower rates [69].

3. MSCs as a Potential Therapy for COVID-19

MSCs were discovered for the first time in mouse bone marrow [70], and have since then been found in many organs [71]. They have been extensively tested and proven effective for many disorders, and they have showed an advantageous potential to treat multiple diseases [72] [73] [74] [75].

MSCs can intervene in injury sites through different mechanisms: they can 1) differentiateinto different cell types [76], 2) repair the damaged cells through cell fusion [77], 3) release paracrine bioactive molecules such as growth and differentiation factors, and chemokines [78], 4) transfer organelles (e.g., mitochondria) and/or molecules through tunneling nanotubes (TNTs) [79], and 5) mediate the transfer of proteins, lipids, DNAs, mRNAs, non-coding RNAs (ncRNAs), carbohydrates, and growth factors by exosomes [80].

Recently, MSCs curative potential has been reported in fighting COVID-19 disease [31] [81] [82]. It was reported that MSCs, cells source was not disclosed in the publication, lacked ACE2 expression [14]. MSCs did not express ACE2 and transmembrane serine protease 2 (TMPRSS2), which is mainly expressed by endothelial cells in respiratory and digestive tracks and facilitates entry and activation of SARS-CoV-2 in host cells [14]. A different study also did not find expression of ACE2 and TMPRSS2 in fetal and adult human MSCs [83]. These results suggest that MSCs could be resistant to COVID-19 [84], which is another expectation from MSC therapeutic potential in battling the virus. Although ACE2 and TMPRSS2 are expressed in oral epithelia cells [85], there is limited report about their expression in DPSCs. Our preliminary unpublished data indicates low expression of ACE2 and TMPRSS2 compared to lung epithelia cells. More experiments are warranted to confirm the observation.

MSCs showed anti-inflammatory properties and they demonstrated to reduce the cytokine storm via paracrine way, and their activities are controlled by chemokines [86] [87]. They are able to decrease inflammation through the release of anti-inflammatory factors or the inactivation of some immune cells [88].

3.1. Potential Role of MSCs in Immune Response

MSCs are endowed with high immune modulatory properties. They communicate with many immune cells of innate or acquired responses, including macrophages, dendritic cells (DCs), T cells, B cells, and NK [89]. The components of the secretome of stem and immune cells represent the most important key play-

ers to decode the biological pathways of any disorder [90] and possibly COVID-19 infection as well [91].

3.1.1. Antigen Presentation

MSCs showed to suppress the migration and maturity of DCs [92]. MSCs suppressed antigen processing and presentation of DCs, differentiation, and maturation of DCs [93] [94]. In addition, MSCs showed to suppress monocyte differentiation into DCs by decreasing the presentation molecules signature and the cytokines secretion. When MSCs are exposed to TNF-α and IFN-γ, they stimulate the over-expression of anti-inflammatory factors essentially the prostaglandin E2 (PGE2) and the programmed death ligand 1 (PDL1), which inhibit the antigen processing by DCs and expansion of cytotoxic, helper, and regulatory T cells and reduce the evolved immune cells [95]. DPSCs, possess stem cell properties and they showed to suppress macrophage functions via the TNF-α/IDO axis, this provided a physiologically pertinent evidence for their innate immunomodulatory activity [96]. MSCs are capable of immune-suppressing the activity and cytokine secretion of neutrophils and macrophages [97] [98], consequently this may reduce the cytokine storm.

3.1.2. Phagocytosis

MSCs showed to modulate the activity of macrophages [99] [100], which exert both pro and anti-inflammatory properties by a direct cell-to-cell contact or by soluble mediators [101]. Chen *et al.* showed that BM-MSCs conditioned medium can suppress phagocytosis [102]. While another study reported that MSCs are able to induce macrophages phagocytosis [79]. In addition, MSCs exhibited a great induction potential to polarize in the polarization of macrophages to an anti-inflammatory profile [101] [103] [104] [105].

Increased concentrations of IL-10 were ensured by IL-6 and hepatocyte growth factor (HGF) secreted by MSCs [106]. IL-10 consequently inhibits the differentiation of monocytes to DCs but switches it to macrophages [107]. Liu *et al.* found released bodies by MSCs able to create a tissue repair through the generation of an anti-inflammatory profile [108]. The anti-inflammatory environment can reduce the inflammation caused by SARS-CoV2.

Another mechanism was employed by the menstrual blood-derived stromal cells (MenSCs) to exacerbate infections is by decreasing the migration of immune cells to the damaged site and suppressing immune clearance [109], this could reduce leukopenia observed in COVID-19. A recent study showed that the co-culture of DPSCs and macrophages decrease pro-inflammatory and increase anti-inflammatory cytokines from macrophages [110].

3.1.3. Apoptosis

MSCs showed to inhibit apoptosis of immune cells. Fadhi *et al.* evaluated the impact of human bone marrow mesenchymal stem cells (BMMSCs) on human immortalized myelogenous leukemia cell line K562 by co-culture [111]. In addition, Gu *et al.* found that MSCs decrease neural apoptosis and improve learn-

ing-memory function in hypoxic–ischemic brain damage (HIBD) rats by inhibiting the TLR2/NFκB signaling pathway [112]. DPSC-EVs showed to reduce cytotoxicity through anti-apoptotic mechanism by upregulating endogenous Bcl-2, and decrease the expression of the pro-apoptotic regulator Bax in Aβ peptide-exposed human neuroblastoma cells [113]. Bax was reported to be expressed in overnight-cultured neutrophils. However, upon co-culture with BMMSCs, the neutrophils showed a significant decrease of Bax expression. MCL-1, a well-known mitochondrial antiapoptotic protein, was upregulated in neutrophils after co-culture with MSCs compared with neutrophils cultured in medium alone [95]. As SARS-CoV-2 has showed to trigger cell pyroptosis [40], [55], the use of MSCs may help to decrease it.

3.1.4. NK Cells Cytotoxicity

NK cells are granular lymphocytes of the innate immune system, implicated in the microbe-infected cells and the immune surveillance of tumors. When stimulated, NK cells release multiple chemokines such as IFN-γ, MIP-1α, MIP-1β, TNF-α, GM-CSF, and chemokines (IL-5, IL-8, IL-10, IL-13) that can regulate other innate and adaptive immune cells [114] [115]. MSCs are considered as powerful inhibitors of natural killer cell proliferation [116] [117]. The co-culture of NK cells with MSCs seemed to impede the cell signaling through cytokines release [118]. Many cytokines (prostaglandin E2 (PGE2), TGF-β1, and IL-6) were secreted by MSCs and showed to hinder the NK cells properties [118] [119]. Along the same line, Sotiropoulou *et al.* found that MSCs showed to reduce the NK cells activation and secretion promoted by IL-2, this interaction sometimes requires direct cell contact, whereas soluble factors exhibited to play an important role, such as TGF-β1 and PGE2 [120]. DPSCs reported to impede NK cells proliferation and to promote apoptosis of activated NK cells also the cytotoxic capacity of NK cells showed to be notably reduced [121]. Severe COVID-19 resulted in an increase in armed NK cells containing high levels of cytotoxic proteins such as perforin [122]. The NK suppression could reduce the cytokine secretion and consequently the cytokine storm.

3.1.5. Cell Mediated Immune Response

Previous studies suggest that MSCs are not particularly capable to modulate the immune response, but they also induce the tolerance toward other transplanted cells [123] [124].

MSCs showed a spontaneous ability to suppress the expansion and function of T-cells ($CD4^+$ and $CD8^+$ T cell subsets) [125] [126] [127] [128] [129]. In inflammatory environment MSCs transform into suppressive cells to reduce the inflammation [130]. In the presence of DCs, MSCs lead the passage from pro-inflammatory Th1 to anti-inflammatory Th2 cells, consequently a secretion profiling modification toward anti-inflammation [131] [132] [133]. Moreover, this inhibition was dose dependent for both $CD4^+$ and $CD8^+$ T-cells. The 24 hours T-cells co-culture with MSCs showed to impact these T-cells activities [130]. MSCs

showed to inhibit Th17 but not Treg differentiation [134]. MSCs induce an immunoregulation toward an anti-inflammatory response by promoting naive T cells into T cells with an anti-inflammatory Treg cells profile and by contributing to generate an immunosuppressive environment via the inhibition of proinflammatory T cells [134] [135] [136].

Moreover, MSCs can communicate with B cells and they affect the plasmablast differentiation also the expansion of reg B-reg cells, which possess an immune-suppressive activity facilitating the immunotolerance [103] [137]. MSCs regulate the proliferation in inflammatory environment, by inhibiting B cell expansion and differentiation by suppressing of transient receptor potential channels (TRP channels) [138], also secreting IL1RA inhibits B cell differentiation [139], and antibodies release of B cells without launching cell death [140].

DPSCs showed to activate compensatory pathways targeting to manage the inflammatory response by regulating pro-inflammatory cytokines in pre-activated T lymphocytes [24]. Another study confirmed that DPSCs can modulate the production of cytokines in vitro and suppress the proliferation of T and B cells [141], which could help to modulate SARS-CoV2 immune response by reducing the cytokine release and the cell migration to lungs and tissue damaging.

3.2. MSCs's Clinical Use for COVID-19 Disease Treatment

3.2.1. MSCs-Cell Based Therapy

Since the identification of the new emerged SARS-CoV-2, more than 100 clinical trials have been submitted to ClinicalTrials.gov and the WHO Clinical Trials Registry Platform (WHO ICTRP) (https://clinicaltrials.gov) to investigate the potential treatment of MSCs and MSCs derived products. Most of these trials have not been yet published. Two clinical trials using dental pulp mesenchymal cells to treat COVID-19 (NCT04336254 and NCT04302519) were submitted to ClinicalTrails.gov, one of the studies is recruiting. However, most of published clinical interventions using intravenous or intramuscular MSCs treatment for both mild and critical types of COVID-19 cases showed improvement in clinical outcomes with some adverse reactions, and demonstrated that MSCs can play a major role in reducing the acute lung injury (ALI) and the respiratory distress syndrome (ARDS) [14] [15] [16] [81] [88] [142] (**Table 1**). Although the published MSCs therapies used stem cells from different sources (umbilical, placental, dental, menstrual, etc.), in different cells doses from one million to 5×10^7 cells given in one, two or three injections, different administration methods (intravenous and intramuscular) and also different infusion time, the MSCs treated patients showed promising pulmonary function improvement and decrease in deaths.

In all the studies, the cytokine storm started to be downregulated few days after MSCs administration. In the study of Leng *et al.* they noticed a cytokine storm's alleviation in three to six days, but a significant improvement was observed in the pulmonary function and symptoms after 2 days from MSCs transplantation (one million cells) [14]. According to Shu *et al.*, 2×10^6 of human

Table 1. Published MSCs clinical studies for COVID-19 treatment.

MSCs source/ number of patients	Severity of the disease	Administration method/dose	Study design/ Intervention model	Concomitant treatment	Outcomes	Adverse events	References
Umbilical/ Cord/47		Intravenous, 3 cycles; 1×10^6 cells/Kg	Multicentre, double-blind, randomized, placebo-controlled trial.	None	No improvement in survival rate and no PaO_2/FiO_2 changes between D0 and D7.	None related to MSCs treatment	[163]
Umbilical cord/1	Severe	Intravenous, 3 cycles; 1×10^6 cells/Kg	None	Convalescent plasma	Inhibiting cytokine storm, promoting the repair of lung injury, and recovering pulmonary function.	None reported	[164]
Umbilical cord/16	Severe and critically ill	Intravenous, 4 cycles; 1×10^8 cells.	Non-randomized	None	Improvement of oxygenation index and in lymphocytes counts, and decrease in pro-inflammatory cytokines levels (IL-1, IL-6, IFN-γ, TNF-α).	None reported	[142]
Umbilical cord/31	Severe or critical	Intravenous, 1 - 3 cycles; 1×10^6 cells/Kg.	Non-randomized	Antibiotics, antivirals, and intravenous immunoglobulin.	Increase in lymphocytes count, decrease in IL-6 and CRP concentrations, and SARS-CoV-2 PCR negative after 10.7 days.	None reported	[165]
Umbilical cord/100	Severe	Intravenous, 3 cycles; 4×10^7 cells.	Randomized, double-blind, and placebo-controlled	None	Decrease in the size of lesion and severity of pulmonary fibrosis by chest CT and improvement in pneumonia and oxygenation.	Reported but no details	[166]
Adipose tissue/13	Severe	Intravenous, 3 cycles; 1×10^6/Kg.	Non-randomized	None	Reduction in CRP, lactate dehydrogenase (LDH), D-dimer and ferritin and increase in B and CD4+ /CD8+T-lymphocyte counts.	None reported	[82]
Umbilical cord/1	Critically ill	Intravenous, 3 cycles; 5×10^7 cells.	Non-randomized	Thymosin α1 and antibiotics.	The counts of $CD3^+$ T cell, $CD4^+$ T cell, and $CD8^+$ T cell remarkably increased to the normal level, pulmonary. Inflammatory reaction was greatly alleviated. Good clinical outcome and good tolerance of allogenic transfer. Transfer out of ICU, and SARS-CoV-2 negative test after 4 days.	None reported	[81]

Continued

Not reported/7	1 critically severe, 4 severe, and 2 moderate	Intravenous, 1 dose 1×10^6 cells/Kg.	Non-randomized	None	The respiratory rate was regulated 4 days after MSCs transplantation. Both fever and tightness of breath disappeared. The plasma C-reaction protein level decreased. The lymphopenia was significantly improved. Overactivated T cells and NK cells nearly disappeared, and the numbers of the other cell subpopulations were almost restored to the normal levels, especially the CD14 + CD11c + CD11bmid regulatory dendritic cell population. The serum pro-inflammatory cytokine TNF-*α* was reduced. The serum levels of chemokines like IL-10 and growth factor VEGF were both increased.	None reported	[14]
Umbilical cord/18	Moderate and severe	Intravenous, 3 cycles; 3×10^7 cells per infusion.	Non-randomized	None	IL-6 exhibited a decline within 3 days. Reduced trend in the levels of IFN-*γ*, TNF-*α*, MCP-1, IL-22, IL-1RA, IL-18, IL-8, and MIP-1 within 14 days. CT scans indicated that patients showed absorption of pulmonary pathological changes and the lung lesions were well controlled within 6 days, and completely faded away within 2 weeks. Recovery.	Two patients receiving UC-MSCs developed transient facial flushing and fever, and one patient developed transient hypoxemia at 12 h post UC-MSCs transfusion.	[15]

Continued

Umbilical cord/12	Severe	Intravenous; 1 dose, 2×10^6 cells/kg	Single-center, open-label, individually randomized trial	Antiviral and antibiotic treatments, glucocorticoid therapy and vasopressors.	The levels of inflammatory factors, including IL-6 and C-reaction protein (CRP), could be rapidly reduced, and the lymphocyte count could return to normal levels in less time. As the patient's chest tightness and shortness of breath quickly improved, arterial blood gas suggested that the oxygenation index could improve. Chest CT scans demonstrated a reduced lung inflammation.	None reported	[88]
Dental pulp/20	Severe	Intravenous; 3 doses; 3×10^7	Single center, two arm ratio 1:1, triple blinded, randomized, placebo-controlled, parallel group.	None	Good clinical outcome and good tolerance of allogenic transfer.	None reported	[22]
Umbilical cord Wharton's jelly/1	Severe	Intravenous; 1 dose, 1×10^6 cells/Kg	Non-randomized	Dexamethasone (2 mg) before intravenous infusion.	The percentage and counts of $CD3^+$ T cell, $CD4^+$ T cell, and $CD8^+$ T cell were increased The levels of plasma CRP and inflammatory factors (IL-6 and TNF-α) were all decreased after the umbilical cord wharton's jelly treatment. Both fever and shortness of breath disappeared on the 2nd day after transplantation.	None reported	[16]
Umbilical cord or placental/11	Critically ill	Intravenous 3 doses, 200×10^6 cells	Non-randomized	Different treatment protocols: hydroxychloroquine, kaletra, azithromycin, ribavarin, favipiravir, vancomycin, colistin.	Significant reductions in serum levels of TNF-a, IL-8, IL-6, IFN-γ and CRP. Four patients who had signs of multi-organ failure or sepsis died in an average of 10 days after the first MSC infusion.	No serious adverse events reported 24 - 48 hours after the cell infusions. Reduced dyspnea was observed One patient showed signs of acute renal and hepatic failure and cardiac arrest development.	[167]
Umbilical cord/24	6 mild to moderate, and 18 moderate to severe	Intravenous; 2 doses, $100 \pm 20 \times 10^6$ cells	Double-blind, placebo controlled, randomized trial.	Heparin, remdesivir, corticosteroids, tocilizmab, hydroxychloroquine.	Inflammatory cytokines were significantly decreased in 6 days. Improved patient survival.	New cardia arrhythmia requiring cardioversion. Worsening hypoxemia.	[17]

Continued

Not specified/23	Severe	10 Infusion; 2 to 3, doses, 10^6 cells/kg	Non-randomized	None	In the MSC group, 80% patients survived to discharge and exhibited good pulmonary function, whereas only 45% of patients in the control group survived to discharge. Decrease of CRP and IL-6. The incidence of kidney injury and hepatic failure in the MSC group did not differ from the incidence in the control group of patients. Patients in the MSC group showed lower mortality than those in the control group (20% vs. 55.6%).	None reported	[168]
Umbilical cord blood derived MSCs/1	Severe	Intravenous 5 doses, 1.5×10^6 per kilogram	Non-randomized	Recombinant human interferon, lopinavir/ritonavir, piperacillin tazobactam and heparin.	Hematological and biochemical indexes, including lymphocytes and renal function improved. Pulmonary static compliance increased significantly and PaO_2/FiO_2 ratio maintained stable.	None reported	[169]
Menstrual blood-derived MSCs/2	Severe	Intravenous 3 doses, 1×10^6 per kilogram	Non-randomized	Ribavirin, arbidol hydrochloride, oseltamivir, and cefoperazone-sulbactam.	MSC transplantation increases the immune indicators (including CD4 and lymphocytes) and decreases the inflammation indicators (IL-6 and CRP). the fraction of inspired O_2 (FiO_2) of the two patients gradually decreased while the oxygen saturation (SaO_2) and partial pressure of oxygen (PaO_2) improved. Chest CT showed that bilateral lung exudate lesions were adsorbed after MSC infusion.	None reported	[170]

Abbreviations: CRP: C-reaction protein; CT: computed tomography; ICU: intensive care unit; MSCs: mesenchymal stem cells; PaO_2/FiO_2 ratio: ratio of arterial partial pressure of oxygen to fraction of inspired oxygen RR: respiration rate; SpO_2: oxygen saturation. COVID-19 infection illness categories; Mild: showing various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging; moderate: showing evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥ 94% on room air at sea level; severe: showing SpO_2 < 94% on room air at sea level, a ratio PaO_2/FiO_2 < 300 mm Hg, respiratory frequency > 30 breaths/min, or lung infiltrates > 50%; critically ill: showing respiratory failure, septic shock, and/or multiple organ dysfunction [171].

umbilical cord mesenchymal stem cell (UCMSCs) per kilogram of weight intravenously administrated to 12 severe COVID-19 patients were able to reduce the CRP and IL-6 from day 3 of transplantation [88]. Multiple cytokines concentrations (IFN-γ, TNF-α, IL-18, IL-8, and MIP-1) noticeably decreased in less than two weeks. The administration of UCMSCs-treated subjects notably reduced the inflammatory cytokines at day 6. A remarkable patient survival rate and recovery time were noted. The use of UCMSC was safe according to this trial [17]. The transplantation of Wharton's Jelly-derived MSCs to severe COVID- 19 pneumonia patient in one dose improved breathing and decreased fever within two days of MSC administration [16].

Some adverse side effects have been reported like facial flushing and fever, allergic rash, liver and kidney failure, new cardia arrhythmia, and worsening hypoxemia. In the study of Lanzoni *et al.*, the use of high dose of UCMSCs (10^8 cells) provoked one case of heart failure [17].

Interestingly, it was demonstrated that priming MSCs showed to be more efficient, Park *et al.* found that HGF-primed MSCs demonstrated a high regenerative potential and an elongated cells surviving [143]. In the submitted clinical trials, we noticed that no stimulating step was added to the therapeutic process. Several studies investigated the co-culture of dental pulp stem cells (DPSCs) and immune cells and their role in reducing the inflammation for COVID-19 patients and showed more anti-inflammatory benefits than DPSCs or immune cells cultured alone [23]. However, in resting conditions, MSCs do not have a high immunomodulatory activity, but when they are stimulated, they show their potential. This leads to the fact that the regulatory properties are not constitutively expressed by MSCs but are related to the process of priming [144].

Also, the preclinical study of Bustos *et al.* reported that BMMSCs treated with ARDS patients serum were more efficient to relieve pro-inflammatory cytokines secretion than unconditioned MSCs [145]. In another study, the activation of BMMSCs with same kind of serum led to a high secretion of IL-1RA and IL-10, reduced the release of inflammatory mediators, upregulated the TLR-4 and vascular endothelial growth factor (VEGF) genes, and launched an important immunoregulation through the prostaglandin E2 (PGE2) release [146].

There are obviously many limitations in the current studies. The small sample size to start with and the loss of treated subjects due to the severity of the COVID-19 during the studies. MSCs seem to be efficient and tolerable by patients in almost all the reported cases in COVID-19 therapy but long-term tracking and follow up information is pending. Future studies on larger pool of patients and long-term studies are required to evaluate the risks associated with MSC therapy, such mal-differentiation, immunosuppression, and instigation of malignant tumor growth [76].

Extracellular vesicles secretion represent another mechanism through it MSCs can regulate the immune response [147]. MSCs derived extracellular vesicles (MSC-EVs) contain heterogenous cargos such as proteins, lipids, DNAs, mRNAs, ncRNAs, carbohydrates, and growth factors [31] [148]. MSC-EVs are important

for cell communication by acting as the delivers of the necessary factors of regeneration, antibacterial activity and immunomodulation [7] [149] [150] [151]. The most important advantages of using exosome-based therapy are 1) cell-free therapy without vascular obstruction, 2) low immunogenicity, and 3) ability to load content of miRNA in exosome [152] (**Figure 2**).

3.2.2. Promising Immunomodulatory and Regenerative Potential of DPSCs

Several clinical and research studies investigate the safety and efficacy of DPSCs in suppressing the cytokine storm and promoting injuries repairing in COVID-19 disease [22] [23] [153]. Likewise, accumulating evidence revealed the powerful properties of DPSCs. They are known for their immunomodulation and regenerative potential, they demonstrated to reduce inflammatory reactions in many auto-immune and inflammatory diseases [96] [154] [155] [156] and to induce tissues regeneration [110] [157] [158]. Moreover, DPSCs showed interesting regenerative and immunomodulatory properties when they are primed or co-cultured with other types of cells. TGF-β1 showed to induce DPSCs differentiation into functional pericyte-like cells [159]. The DPSCs also showed to secrete important amounts of prostaglandin E2, which is a key mediator for the anti-inflammatory activity and it contributes to the resolution of inflammation, and

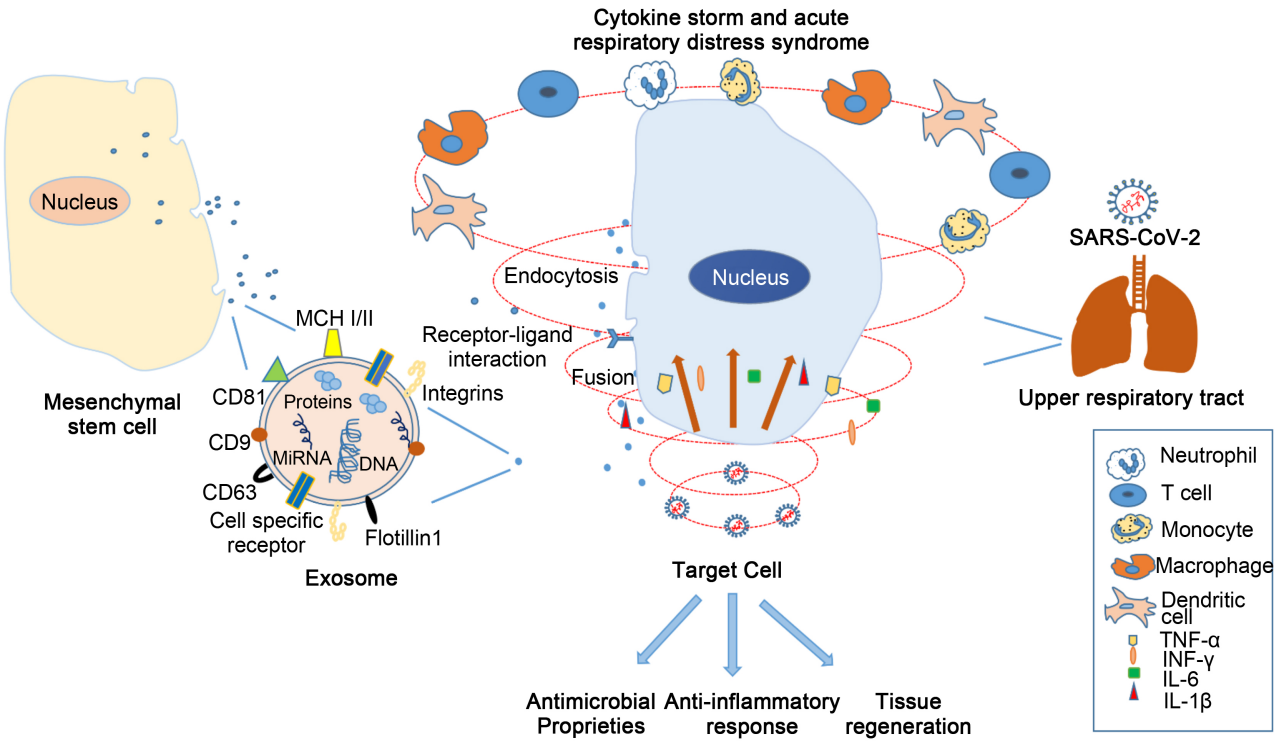

Figure 2. Mechanisms of action of MSCs against COVID-19 infection. COVID-19 patient can develop serious cytokine storm and ARDS. Immune cells are activated, pro-inflammatory cytokines (IL-6, TNF-α, etc.) are over-released, lung cells are injured, and multiple organs fail. MSCs, through exosome, can induce an anti-inflammatory reaction and a cytokine storm reduction, a tissue regeneration, and an antimicrobial activity. Abbreviation: ARDS: acute respiratory distress syndrome; MSCs: mesenchymal stem cells.

they maintained their immunomodulatory activities even upon differentiation [160].

A study investigated the co-culture of DPSCs and immune cells and their role in reducing the inflammation for COVID-19 patients and showed more anti-inflammatory benefits than DPSCs or immune cells cultured separately [23]. The potent immunomodulatory functions of DPSCs due to their soluble factors and cytokines showed to play a crucial role in clinical cell therapy by T-lymphocyte function inhibition and upregulation of T cell regulatory (Tregs) stimulating immune tolerance [161] [162].

4. Conclusion

SARS-CoV-2 continues to grip the world with high infection rate, uncertain long haul symptoms in recovered patients, and an economic burden. Since the available vaccines do not protect from a re-infection with SARS-CoV-2, developing therapies to boost host immune systems to fight the virus infection and treat ALI and ARDS still seem to be of high priority. MSCs and especially DPSCs could be an interesting therapeutic candidate, since many phase-1 and 2 trials have shown promising results. However, consistent studies are still needed to reveal the whole MSCs therapeutic mechanism and to ensure their safety and efficacy.

Acknowledgements

This work was supported by Tobacco-Related Diseases Research Program Grant T30IP0917 from Regents of the University of California.

Funding Information

This work was supported by Tobacco-Related Diseases Research Program Grant T30IP0917 from Regents of the University of California.

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Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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