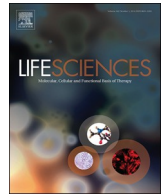




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Mesenchymal stem cell therapies for COVID-19: Current status and mechanism of action

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ABSTRACT

The outbreak of COVID-19 in December 2019, has become an urgent and serious public health emergency. At present, there is no effective treatment or vaccine for COVID-19. Therefore, there is a crucial unmet need to develop a safe and effective treatment for COVID-19 patients. Mesenchymal stem cells (MSCs) are widely used in basic science and in a variety of clinical trials. MSCs are able to engraft to the damaged tissues after transplantation and promote tissue regeneration, besides MSCs able to secrete immunomodulatory factors that suppress the cytokine storms. Moreover, the contribution of MSCs to prevent cell death and inhibit tissue fibrosis is well established. In the current review article, the potential mechanisms by which MSCs contribute to the treatment of COVID-19 patients are highlighted. Also, current trials that evaluated the potential of MSC-based treatments for COVID-19 are briefly reviewed.

1. Introduction

Over the past decade, the world has experienced the prevalence of life-threatening pandemic of coronaviruses, the severe acute respiratory syndrome (SARS) in 2002, and the Middle East respiratory syndrome (MERS) in 2011. In early 2020, the outbreak of the novel coronavirus (2019-nCoV) has led to a global pandemic known as novel coronavirus disease (COVID-19) after originating in Wuhan, China. The 2019-nCoV is highly contagious with a long incubation period and strong infectivity [1]. From a pathological perspective, the COVID-19 is highly pathogenic with severe pneumonia associated with rapid virus replication [2]. As of April 30, 2020, despite great efforts from scientific and clinical communities, there is no suitable therapy or vaccine for COVID-19 and the therapeutic strategies are generally to manage rather than cure this disease.

Current studies have shown that similar to SARS and avian influenza, cytokine storm is the main immunopathogenesis mechanism of COVID-19 which eventually develop acute respiratory distress

syndrome (ARDS) [3].

Stem cell-based therapies, in particular mesenchymal stem cells (MSCs), have shown great potential in the treatment of a variety of diseases [4,5]. MSC-based therapy has been used for ARDS due to the ability of MSCs to secrete anti-inflammatory, anti-fibrosis, and anti-apoptosis cytokines, which eventually dampen the cytokine storm [6,7]. Together, current literature suggests that ARDS might be cured with MSCs. Therefore, in the current review paper, the clinical characteristics of COVID-19 will be shortly highlighted, then the opportunities and challenges in the application of MSCs for the coronavirus induced-ARDS are discussed.

2. Immunopathology of COVID-19

The envelope-anchored spike glycoprotein on the coronavirus attach to the angiotensin-converting enzyme 2 (ACE2) and mediates coronavirus entry into host cells [8]. After membrane fusion, the viral RNA genome is released into the cytoplasm, and the uncoated RNA

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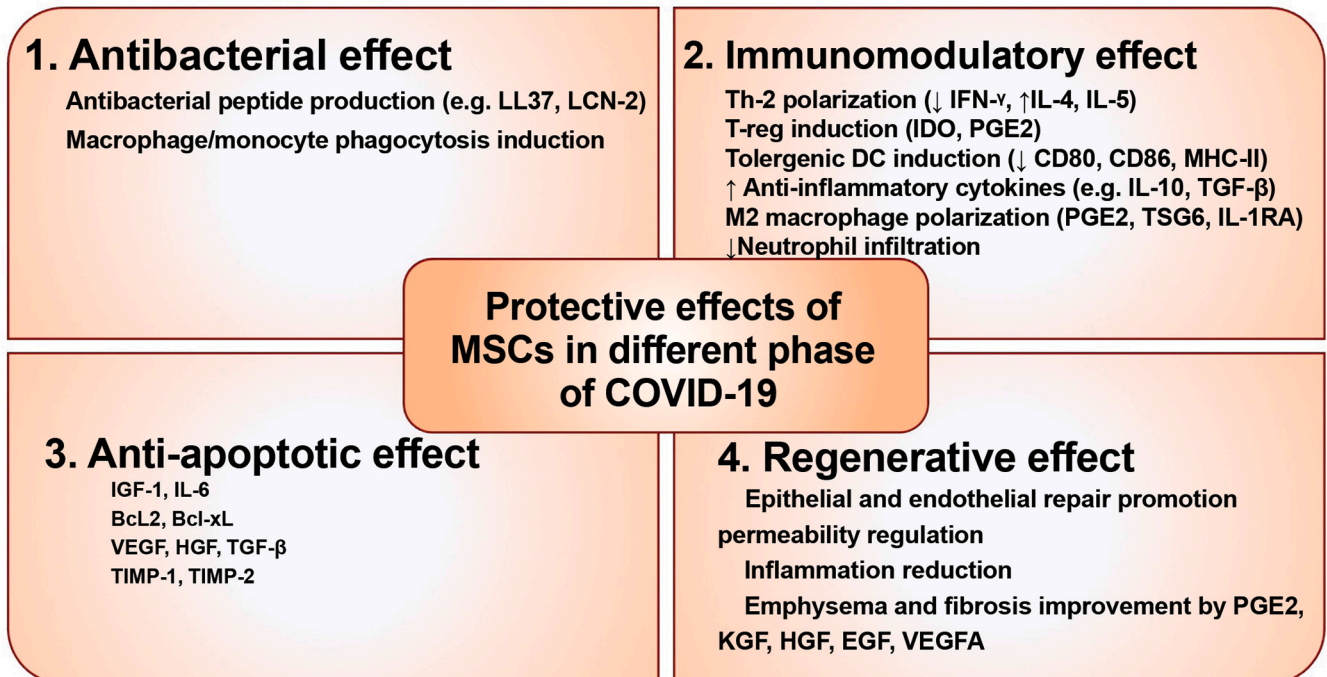
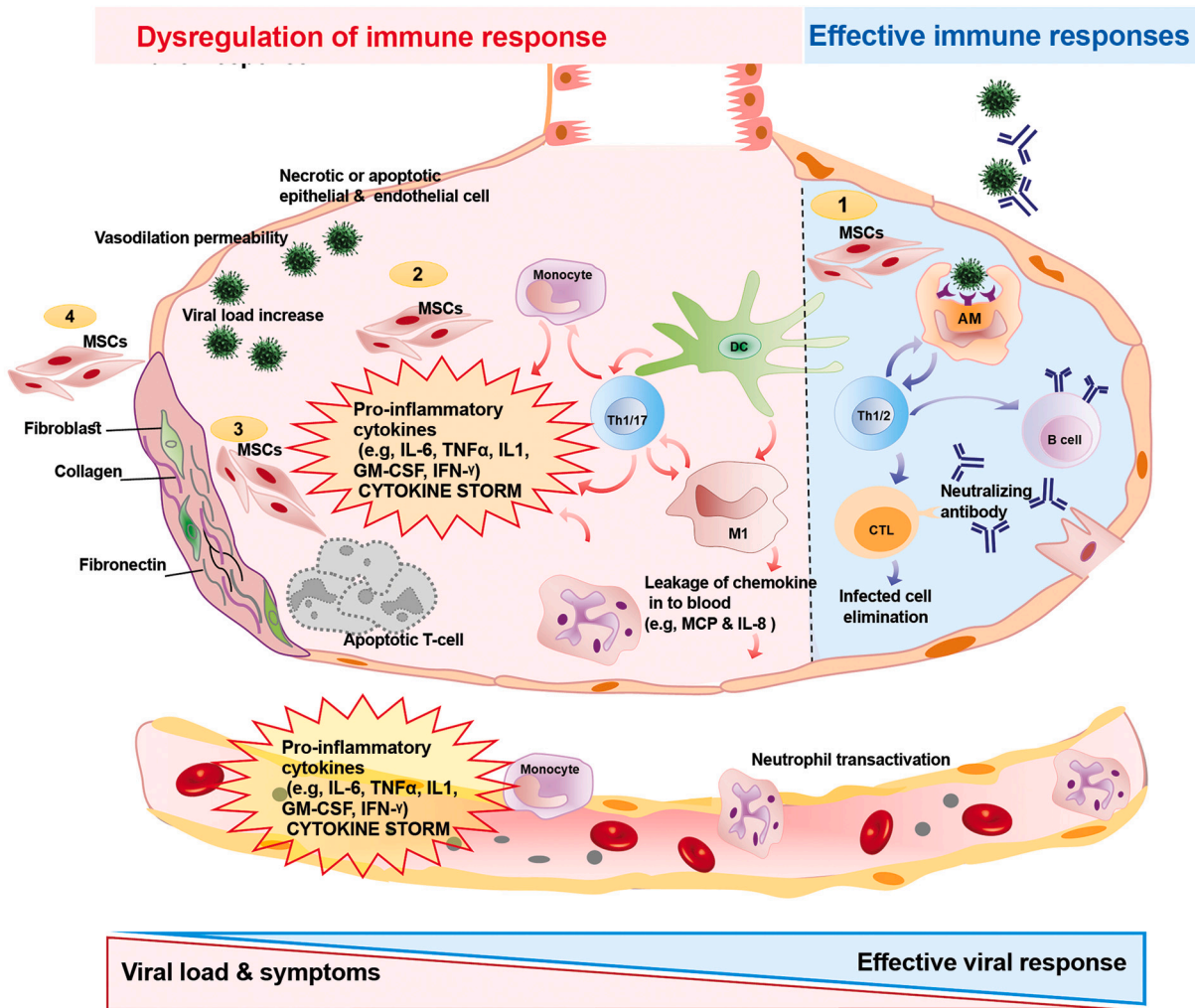


Fig. 1. The immunopathogenesis of COVID-19. The mechanism of actions of mesenchymal stem cell therapy for the treatment of COVID-19.

translates into two polyproteins and structural proteins. The newly formed genomic RNA, nucleocapsid proteins and envelope glycoproteins assemble in the endoplasmic reticulum (ER) and golgi apparatus and form viral particle buds [8]. The virion-containing vesicles then fuse to the plasma membrane and release the virus [10].

The immune system plays an important role in the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Formation of an appropriate innate immune response in the early stages of the disease which is followed by an effective adaptive immune response limits the progression of the virus from reaching the alveoli and prevents tissue damage. In this case, the virus causes a mild to moderate respiratory disease and patient recovers without requiring special treatment [10]. But if the adverse immune responses are formed and the virus spreads in the lungs, then severe inflammatory responses and cytokine secretions are induced followed by an extensive cell-mediated immune responses to remove the infected cells (Fig. 1). This situation will contribute to the pulmonary edema, dysfunction of air-exchange, as well as ARDS [9,11]. The virus may also enter the bloodstream, and inflammation spreads throughout the body, causing septic shock and vital organ failure especially those organs with high ACE2 expressions such as liver and kidneys [9–11]. Although the protective or destructive immune responses are still being investigated, current evidence support the following immune-related pathogenic factors [10].

2.1. HLA polymorphism

Human leukocyte antigens are among the most polymorphic genes that regulate immune responses against self and non-self-antigens. The quantity and quality of the epitopes presented by HLA molecules affect the outcome of cytotoxic or helper T cells activation in infectious disease [12]. The protective immune response will appear against viral infections, if HLA's present conserved viral epitopes instead of mutated or variable parts and enhance lymphocyte clonal expansion [13]. Different studies confirmed the effective role of HLA in the development of adequate immune responses against influenza, human immunodeficiency virus, and Hepatitis C virus infections [13,14]. Although HLA alleles affecting COVID-19 resistance or susceptibility have not yet been identified, the previously known HLAs in SARS-CoV and MERS-CoV infection are suggested to be involved in COVID-19. HLA-B*4601, HLA B*0703, HLA-DR B1*1202, and HLA-Cw*0801 alleles are associated with the susceptibility to SARS-CoV infection while HLA-DR0301, HLA-Cw1502, and HLA-A*0201 reduced the risk of infection. Also MHC II molecules, such as HLA-DRB1*11:01 and HLA-DQB1*02:0 increase the risk of MERS-CoV infection [8].

2.2. Lymphopenia

The reduction of lymphocyte to less than 1.0×10^9 cell per liter in the peripheral blood is called lymphocytopenia. The changes in the lymphocyte count are among the indicators of both viral and non-viral infections and often used to determine the severity of infection [15,16]. Lymphopenia is caused by an excessive infiltration of lymphocytes into the infected organs and an imbalance in the proliferation and death of lymphocytes [17].

Dysregulated or impaired immune responses against infectious agents terminated to strong systemic inflammation and induces apoptotic death of lymphocytes. The previous study demonstrated that an increase in Fas-L expression on plasmacytoid dendritic cells induces apoptosis of CD8+ cytotoxic lymphocytes in lethal H5N1 influenza infection [18]. Monitoring the dynamic changes in the lymphocyte count of blood samples of dead and cured COVID-19 patients confirmed the decisive role of lymphocyte depletion in disease progression [19]. Therefore, by measuring the percentage of peripheral blood lymphocytes, the severity of the disease and the effectiveness of treatments can be determined. Moreover, the proliferation of viruses in lymphocyte

can induce lymphocyte apoptosis and contribute to the reduction of lymphocyte levels in the blood [20,21]. Soluble Fas ligand, inflammatory cytokines, and glucocorticoids are among the indirect inducers of apoptosis in lymphocytes in SARS-CoV-2 infection [20].

2.3. T cell exhaustion

The appropriate function of cytotoxic T lymphocytes is the main mechanism to eliminate virally infected cells and reduce viral dissemination. However, if the lymphocytes become exhausted and fail to reduce the viral load, the patient experience a progressive viral infection, tissue damage, or chronic infection. High viral load, expression of inhibitory receptors, and suppressive cytokines are among the inducers of T cell exhaustion [22]. Different studies showed the functional exhaustion of T cells in COVID-19 patients. An increase in the expression of NKG2A, PD-1, and Tim-3 inhibitory markers and decrease in the levels of IFN- γ , IL-2, granzyme B, and TNF- α production were reported in the T lymphocytes in COVID-19 patients after recovery [23,24].

2.4. Antibodies

While the mechanistic effects of antibody protection in COVID-19 patients have not yet been well established, the high level of neutralizing antibodies against S protein was found after the infection in the patient's blood [25]. Recently, it was reported that antibodies through binding to the receptor-binding domain (RBD) of the S protein can block the virus interactions with ACE2 protein [26,27].

However, both specific and non-specific antibodies can interact with FC receptors or complement receptors and increase virus entry and proliferation [28,29]. This pathogenic effect of antibodies has been confirmed in the severe forms of COVID-19 disease. Different experiments demonstrated the direct correlation between increased IgG levels and disease progression in COVID-19 patients [30,31].

2.5. Cytokine storm

The formation of a non-protective inflammatory response in infections leads to uncontrolled systemic inflammatory responses which are characterized by an increase in the pro-inflammatory cytokines and chemokines secretion that is called cytokine storm [32]. During these process monocytes, macrophages and neutrophils are being activated in the bloodstream and release the pro-inflammatory cytokines that disrupt the endothelium barrier and extravagate to different organs. The activated CD4+ T cells differentiate to Th1 cells and contribute to a delayed inflammatory response, and also contribute to the activation of cytotoxic CD8+ T cells and Th17 cells which could induce excessive inflammatory responses that are associated with increased cytokine secretion such as IL-6, interferon-gamma (IFN- γ), and granulocyte-macrophage colony-stimulating factor (GM-CSF) [34]. GM-CSF can activate monocytes to further release IL-6 and other factors that lead to the formation of a cytokine storm followed by ARDS which is the leading cause of death in patients with severe COVID-19 pneumonia [33,34].

3. Cytokine storm is an important factor in the COVID-19 pathogenesis

The second stage of COVID-19 pathogenesis is the result of an imbalance between inflammatory and anti-inflammatory cytokines from the patient immune system in response to the viral infection [35]. In the COVID-19 patients, this contributes to a cytokine storm in the lungs. ICU patients with COVID-19 have shown higher plasma levels of inflammatory mediators such as IL-2, IL-6, TNF- α , granulocyte colony-stimulating factor (G-CSF), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1- α (MIP-1 α) and interferon-gamma inducible protein 10 kDa (IP-10) [36].

4. Treatment of COVID-19

As of April 30, 2020, there is no effective therapy or vaccine for COVID-19 infection and current treatments are mainly supportive approaches including oxygen therapy, fluid management and the use of a broad spectrum of antibiotics to inhibit secondary infection. Moreover, several antiviral agents have been repurposed to be used against COVID-19 [8,10]. Here, the major treatment approaches for COVID-19 are briefly highlighted.

4.1. Corticosteroid and inflammatory blocker factors

Nonsteroidal anti-inflammatory drugs have been proposed for COVID-19 treatments. However, recent studies have shown that corticosteroids which are routinely used for influenza infection are not effective enough for COVID-19 [36–38]. Moreover, previous studies reported no therapeutic benefits for corticosteroids in SARS and MERS infections, and were associated with complications such as hyperglycemia and avascular necrosis [39]. The effectiveness of corticosteroids in COVID-19 is controversial, a recent study reported that dexamethasone, is able to reduce the mortality rate of COVID-19 patients who receive invasive mechanical ventilation or oxygen [40].

Monoclonal antibodies against inflammatory mediators have been proposed as potential agents for COVID-19 treatment [39]. Some monoclonal antibodies or immunomodulatory agents have been previously tested in clinical trials for the treatment of cytokine storm-related diseases, including anakinra (IL-1 blockade), bevacizumab (anti-vascular endothelial growth factor), eculizumab (antibody inhibiting terminal complement) and blocking the gamma interferon and Janus kinase/STAT signal transduction pathway [39,41,42]. Tocilizumab, a FDA approved IL-6 receptor antagonist, previously used to manage the cytokine syndrome and acute lymphocytic leukemia, has been used in the patients with COVID-19 pneumonia with promising outcomes [38,39,43]. At this point, the use of these drugs for COVID-19 requires further investigation [11,44].

4.2. Serum of recovered patients

In addition to active immunity through the vaccine, immunity can be achieved through the direct injection of sera of the patients recovered from COVID-19. It was shown that convalescent plasma of patients recovered from SARS and influenza viruses' infections has therapeutic effects without adverse events [45,46]. This treatment plan is now included in the treatment program for the patients with new coronavirus and related to the level of neutralizing antibody titer in the extracted serum, nevertheless, its clinical application is also limited [33]. Despite the beneficial effects, this approach has several limitations, antibodies could lead to the excessive stimulation of immune response which may cause cytokine secretion syndrome and life-threatening toxicity. In addition, the antibody concentration in the blood is very low and makes it challenging to provide enough antibody for the treatment [44].

4.3. Chloroquine and hydroxychloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ), conventional drugs for malaria infection therapy, were used for COVID-19 patients [3,39]. Several possible mechanisms have been suggested for their actions, one is the inhibition of the virus entry through changing the ACE2 glycosylation [47]. Besides, through increasing the pH of endosomes and lysosomes in the antigen-presenting cells (APC), and through the suppression of T cells activation and cytokines production by these cells [47]. Diarrhea and vomiting are common side effects of these two drugs. Moreover, it has been known that having high blood pressure and diabetes worsens in COVID-19 conditions. Therefore, the application of CQ or HCQ with the drug used for high blood pressure and

diabetes may result in life-threatening complications. Although HCQ has fewer side effects, the prolonged and overdose use of HCQ results in critical side effects [36,47]. Although some studies have noted the therapeutic effects of HCQ, the evidence of the benefits and limitations of this drug for the treatment of COVID-19 patients is insufficient and very conflicting [48].

5. Stem cell-based therapies for inflammatory mediated disorders

Currently, numerous clinical trials are launched to investigate potential therapies for COVID-19 patients [39]. In the meantime, MSCs-based therapy has been proposed for COVID-19. MSCs from a variety of sources have been proposed as a potential treatment for many diseases [49–51]. MSCs would appear to have some attractive therapeutic potential to the COVID-19 owing to their powerful anti-inflammatory and immunoregulatory abilities. MSCs can engraft to the damaged tissues after transplantation and contribute to immune modulation and tissue regeneration [52–55]. Mechanistically, MSCs are involved in the down-regulation of acute-phase responses such as the inhibition of abnormally activated T lymphocytes, macrophages, and pro-inflammatory cytokines secretion, thereby could reduce the occurrence of cytokine storm [56]. Moreover, MSCs can inhibit cell apoptosis, and promote endogenous tissue repair and release antimicrobial molecules that can potentially treat the major abnormalities. In contrary to what could be achieved by targeting any intermediaries' single mediator (e.g. monoclonal antibody against TNF, IL-6), MSCs in addition to reducing excessive inflammation, increase the clearance of pathogens [50,55–57]. The safety and effectiveness of MSCs have been documented in several clinical trials [50,58–60].

Currently, MSCs have been applied in numerous trials particularly in the context of inflammatory-mediated disorders [54]. Therefore, it is expected that MSC-based therapies to be effective in the treatment of COVID-19 patients.

5.1. Mechanisms of MSCs-mediated immunomodulation

It is suggested that immunological therapy may be effective in COVID-19 patients [6]. However, since the virus can stimulate the extensive cytokine storm in the lungs, the inhibition of only one or a few inflammatory factors may not be an effective strategy. The immunomodulatory properties of MSCs have become increasingly relevant for clinical use. MSCs can be effective in the inhibition of cytokine storm through their immunomodulatory properties, which is coordinated via the cell-cell interactions and the release of soluble factors [6]. These two mechanisms modulate the proliferation and activation of T cells and induce the polarization of the mononuclear cells to an anti-inflammatory phenotype [61]. Overall, MSCs can inhibit T cell activation through several immunomodulatory factors (e.g. transforming growth factor-beta 1 (TGF- β), prostaglandin E2 (PGE2) and HLA-G5), and membrane-bounded molecules (e.g. PD-L1, VCAM-1, and Gal-1) [34,35]. MSCs also increase regulatory T cells (TReg) and anti-inflammatory TH2 cells. Also, NO and IDO released by MSCs suppressed the T cell cytokine production [62]. The suppression of NK cell cytotoxicity with a decrease in the expression of IFN- γ is another regulatory mechanism of MSCs. Besides, MSCs able to prevent the maturation of dendritic cells (by downregulating the surface expression of CD80, CD86, and MHC class II molecules), thus retaining the DCs in a tolerogenic phenotype and also induce anti-inflammatory M2-macrophage polarization with the increased levels of PGE2, TSG-6, and IL-1RA [62,63]. While many of the identified factors have been used individually to inhibit immune responses, MSCs able to establish an immunomodulated environment via the secretion of many immunomodulatory factors. For example, compared to monoclonal antibodies, the MSCs can simultaneously have a synergistic effect on several cytokines. The unique immunomodulatory property of MSCs is reflected in many clinical trials, it has been shown that MSCs reduce the

inflammatory responses and defend the host against cytokine storm with lowered mortality, without serious side effects [7,62,63]. As a result, MSCs-therapy has emerged as an attractive strategy through several favorable changes in the management of respiratory models such as H7N9-induced ARDS [58,64,65]. Since H7N9 and COVID-19 have similar complications, therefore MSCs-therapy could be an alternative approach in COVID-19 treatment [66].

5.2. Anti-apoptotic properties of MSCs

Apoptosis is a host defense mechanism against infectious agents and plays a central role in the host-pathogen interactions. Apoptosis was observed at different stages of viral infections in SARS patients [63]. Lymphopenia due to T-cell depletion and exhaustion of immune cells by apoptosis has been observed in COVID-19 patients [24]. Therefore, the effective control of apoptosis in COVID-19 patients is critical. MSCs able to prevent cell apoptosis which could be the result of hypoxia, chemical agents, mechanical damage, or radiation. For example, the anti-apoptotic effects of MSCs have been proved in cardiac ischemic, as well as in neural and pulmonary disorders [4]. For example, keratinocyte growth factor (KGF) and hepatocyte growth factor (HGF) released from MSCs protect alveolar epithelial cells from apoptosis with the increased expression of Bcl-2 and inhibition of HIF1 protein [67]. Moreover, in the hypoxia-related apoptosis, MSCs induced the expression of some factors such as vascular endothelial growth factor (VEGF), HGF and TGF- β 1 that can reverse the apoptosis of endothelial cells [45]. Other factors are also involved in the anti-apoptotic effect of MSCs, including insulin-like growth factor-1 (IGF-1) and IL-6 that lead to elevated levels of secreted frizzled-related protein 2 (SFRP2), an important anti-apoptotic mediator in fibroblast-like cells [4].

5.3. Mesenchymal stem cells in tissue repair and regeneration

MSCs contribute to tissue regeneration and repair due to their unique feature in reducing abnormal immune responses, ability to differentiate into the target tissues or secretion of some factors which induce host reparative/regenerative mechanisms [68]. The MSC-secreted factors able to promote tissue repair via supporting the growth and differentiation of local stem/progenitor cells, and through the regulation of extracellular matrix molecules deposition, stimulating the anti-scarring pathways, and inducing the neovascularization [69,70].

In the respiratory diseases, not only the elimination of virus but also the repair of the damaged tissues and restoration of lung tissues are required. ARDS is characterized by disruption of the alveolar-capillary membrane barrier, edema, hyperplasia, and pneumocystis with inflammatory cellular infiltration [71]. Therefore, it is necessary to use new drugs that not only inhibit the inflammation but also stimulate the regeneration of damaged alveolar epithelial cells. MSCs can be considered as a promising treatment option in pulmonary disorders due to their immunoregulatory effect and their potential to differentiate into the lung cells [52].

The beneficial effects of MSCs in ARDS models and in clinical trials have been shown previously [72]. MSCs secrete paracrine soluble factors such as angiopoietin-1 (ANGPT1), epidermal growth factor (EGF), vascular endothelial, PGE2, HGF, VEGFA, KGF and interleukin-10 (IL-10) that can promote epithelial and endothelial repair, increase alveolar fluid clearance, regulate lung epithelial and endothelial permeability and reduce the inflammation in the patients with ARDS-injured lungs [73]. MSCs' derived KGF and HGF have shown beneficial effects in the emphysema and pulmonary fibrosis in the acute lung injury (ALI) model [74].

5.4. Antibacterial properties of MSCs

The antibacterial properties of MSCs are mediated through, 1) the secretion of soluble mediators to decrease bacterial count and improve

the antimicrobial response of immune cells, or 2) the suppression of pro-inflammatory cell migration into the infected tissues.

MSCs through Toll-like receptor (TLR) signaling and crosstalk with immune cells restore the balance between pathogens elimination at an early phase of an inflammatory response, and inflammation suppression to improve the homeostasis and initiate tissue repair [75]. Because of the compatibility of these features with the COVID-19 pathogenesis, MSCs-therapy could be considered as a promising approach.

The therapeutic effects of MSCs in reducing mortality, improving organ function, and also reducing the bacterial load by releasing antimicrobial peptides (such as human cathelicidin (LL-37) and lipocalin-2 (LCN-2)) and enhancing monocyte phagocytosis were shown in different lung injury animal models [54,75].

Because COVID-19 infection is associated with an increased risk of infection with other respiratory viruses, fungi, and bacterial infection, therefore the antibacterial treatments are essential [76]. Antibiotic treatment significantly reduces the bacterial load in the body, but unable to induce tissue repair [77]. However, MSCs have multiple protective mechanisms through the secretion of several paracrine factors which not only contribute to bacterial clearance, also modulate the immune response and restore the epithelial integrity and facilitate repair/regenerative processes [77]. Of importance, MSCs can prevent the development of drug-resistant microbes, a problem with conventional antibiotics [74,76].

The functional mechanism of MSCs is relying on their paracrine effects through exosome secretion. Exosomes as a membrane vesicles can be released from a variety of cells and are capable to deliver microRNAs (miRNAs), lipids and proteins to the cells [78]. miRNAs as a class of non-coding RNAs, regulate the gene expression by targeting mRNAs. It has been shown that MSCs are involved in physiological and pathological processes through miRNAs derived from exosomes [79]. Moreover, the therapeutic effect of miRNAs derived from MSC' exosome have been shown in several diseases including Parkinson's, transmissible spongiform encephalopathy, spinal cord injury and autoimmune diseases [78,80]. It has recently been reported that miR-199a, miR-145 and miR-221, from UCBMSC-derived exosomes, are involved in inhibiting hepatitis C virus (HCV) RNA replication [78].

6. Clinical applications of mesenchymal stem cells

Clinical and preclinical researches have focused on the potential role of MSC in reducing the mortality rate, inflammation, and lung injury in ARDS [55,81–84]. The safety and efficacy of MSCs in ARDS have been established in numerous clinical trials [61,72]. MSC therapy seems to be effective in ARDS due to its low immunity, polytropic effects, and the ability to migrate to the injury sites [64]. MSCs able to reduce the levels of C-reactive protein (CRP) modulate the over-activation of cytokine-secreting cells in COVID-19 patients [7].

MSCs reduce the host's damage caused by inflammation while increasing the host's resistance to sepsis and ARDS due to the enhanced host cell phagocytosis, increased bacterial clearance, and antibacterial peptide production [55,85]. MSCs also express several interferon-stimulated genes (ISGs) that are known to show the anti-viral activities [86]. MSCs contribute to lung tissue regeneration in ALI and ARDS diseases via the secretion of cytoprotective agents [57,61,82]. Angiopoietin and keratinocyte growth factor secreted from MSCs able to restore alveolar epithelial and endothelial cells in ALI and ARDS models [82,87]. The ability of MSCs to reduce the pathological deviation such as the accumulation of lung collagen and fibrosis, and reducing the levels of matrix metalloproteinases have been demonstrated [88]. Therefore, it could be effective in the pulmonary fibrosis in the COVID-19 [86]. MSCs have become an exciting candidate for COVID-19 induced ARDS due to their immunomodulatory effects, regenerative properties, the controlling the oxidative damage, protection of the endothelium, and the epithelium and their antibacterial effects [88]. Increasing studies related to MSC therapy in the COVID-19 outbreak have

promise results and indicate their possibility of effective in this infection [89–92]. However, these studies are limited and future clinical trial is undeniable [93]. Despite early promising results, the limitations related to MSC therapy in previous studies including the route of injection, should not be forgotten. Intravascular coagulation and thromboembolism are the causes of mortality in patients with COVID-19 and MSCs express levels of pro-coagulant tissue factor (TF/CD142), and this may makes their application challenging [93]. The immunocompatibility tests and administration of an alternative non-IV injection could be effective to overcome this challenge [93].

7. Clinical applications of mesenchymal stem cells for COVID-19

Recently, one study reported the clinical outcome of a 65-year-old female COVID-19 patient with severe pneumonia, respiratory and multiorgan failure who was treated with allogeneic human umbilical cord blood-derived mesenchymal stem cells (UCBMSCs), for three times (5×10^7 cells each time) [94]. After the second dose, the patient was off the ventilator and well tolerance was observed, and the measured parameters returned to the normal levels. Two days after the third injection, the patient was transferred out of the ICU and her test was confirmed negative for coronavirus. Although this study was reported on one case and extensive trials are needed, but indicated that MSCs could be applicable for COVID-19 infection or could be applied in combination with other therapies for COVID-19 [94].

Another study was investigated the impact of MSCs therapy in 7 patients with COVID-19 pneumonia (one patient with critically serious, 4 patients with serious and 2 patients with common clinical symptoms). Treatment was a single dose of clinical-grade MSCs (1×10^6 cells/kg), intravenously [6]. Patients were monitored for 14 days after MSCs transplantation. On the second day after the injection, pulmonary function and symptoms of patients were improved. The results showed that after MSCs transplantation, the peripheral lymphocytes were increased and CRP and inflammatory cytokines significantly decreased, whereas IL-10 and regulatory DC cells were increased. Although small sample size and short-term follow-up are some of the limitations of this study, the therapeutic potential of MSCs in COVID-19 patients with severe conditions was reported and no complications were noted in the treatment group [6].

Recently, several MSC-based clinical trials for COVID-19 have begun in numerous countries (Table 1). A considerable number of clinical trials are currently underway that investigating different aspects of MSC (NCT04252118), (NCT04288102), (NCT04341610), (NCT04361942), (NCT04416139), (NCT04428801), (NCT04444271), (NCT04392778), umbilical cord blood-derived mesenchymal stem cells (UCBMSCs) (NCT04269525), (NCT04293692), (NCT04273646), (NCT04339660), (NCT04429763), (NCT04437823), (NCT04456361), (NCT04490486), (NCT04457609), allogeneic umbilical cord lining stem cells (ULSC) (NCT04494386), bone marrow-derived mesenchymal stem cells (BMMSCs) (NCT04346368), (NCT04377334) and Wharton's jelly-MSCs (WJMSCs) (NCT04313322) (NCT04333368), (NCT04390152), NestCell® (NCT04315987), dental pulp MSCs (NCT04302519), (NCT04336254), adipose-derived mesenchymal stem cells (AMSCs) (NCT04366323), (NCT04352803), (NCT04362189), (NCT04348461), (NCT04348435) and autologous adipose-derived mesenchymal stem cells (AMSCs) (NCT04349631), placenta-derived MMSCs (PMMSC) (NCT04461925) and allogenic pooled olfactory mucosa-derived mesenchymal stem cells (NCT04382547) (Table 1).

Most studies have examined intravenous administration MSC in COVID-19, but the purpose of a pilot clinical trial, single-arm design, open-label, combined interventional clinical trial, is to explore the safety and efficiency of aerosol inhalation of the exosomes derived from allogeneic adipose-derived MSCs (MSCs-Exo) in the treatment of patients with severe COVID-19 (NCT04276987).

CAStem is an injectable product composed of immunity- and matrix-regulatory cells (IMRCs), also named as M cells, differentiated from

clinical-grade human embryonic stem cells (hESCs). A phase I/II trial will be done to evaluate the safety and efficacy of CAStem for the treatment of severe COVID-19 associated with or without ARDS. CAStem will be cryopreserved and transported to the clinical site using liquid nitrogen vapor shipping vessels (< -150 °C). Before the injection, CAStem will be reconstituted in normal saline. In this study, 3 cohorts with 3 patients/cohort will receive 3, 5, or 1×10^7 cells/kg (NCT04331613).

8. Limitations and considerations in mesenchymal stem cell therapy in COVID-19 patients

Eligibility is one of the first limitations of MSCs therapy. Although all patients with confirmed 2019-nCoV infection using RT-PCR laboratory tests and pneumonia with chest radiography can be a volunteer for MSC therapy, not all of them necessarily have the eligibility for cell therapy. Patients with a history of a malignant tumor or other serious systemic diseases, organ transplantation, chronic immune suppression, severe allergies, co-infections of HIV, tuberculosis, influenza and other respiratory viruses, pregnant and lactating women will exclude from the clinical trial. Besides, some eligible patients are unable to participate in post-cell therapy evaluations due to the severity of the disease and the use of invasive ventilation are ignored.

Concomitant use of conventional drugs in COVID-19 patients with MSCs therapy makes it difficult to interpret subsequent evaluations, side effects, and effectiveness of MSCs therapy. Remdesivir and dexamethasone as common antiviral and anti-inflammatory drugs, administered to COVID-19 patients can affect clinical signs, mortality, and immunological factors. Therefore, the results obtained after cell therapy cannot be generalized to the effect of MSCs alone. Finally, the lack of a standard therapeutic protocol leads to variation in the effective parameters in cell therapy including origin of MSCs, stem cell pre-conditioning, route of administration, dose and frequency of MSCs transplantation and appropriate stage of disease for MSCs therapy. All of these mentioned factors will influence MSCs trafficking, proliferation, differentiation, cell-cell and cell-microenvironment interaction and soluble factor secretions that terminated to wide range of immunomodulation in different clinical trials. The mentioned points should be considered in designing the appropriate method of MSCs therapy and interpreting the obtained results in clinical trials. Fig. 2, represented the various aspects that should be considered in MSCs-based therapy.

9. Conclusions

The COVID-19 pandemic presents a serious and urgent healthcare crisis. Numerous clinical trials are launched to find out an effective treatment for this highly infective disease. However, no suitable therapy exists to date. Preclinical data suggest that MSCs through multiple protective mechanisms such as anti-inflammatory, anti-microbial, and regenerative properties could be used to treat COVID-19 patients. Feasible delivery of MSCs and MSCs derived exosomes to the lung and its potent immunomodulatory activity have prompted clinical trials to treat COVID-19 patients, in various clinical centers around the world. Despite available evidence for the therapeutic potential of MSCs therapy, there is no comprehensive information on the effectiveness of this method in overcoming COVID-19 disease. Most clinical trials are in phases I and II, and the results of this therapeutic method on the disease progress are not yet clear. However, the broad spectrum of MSCs effect on the immune system, suggests it as a good candidate for the combination therapy of infectious diseases such as COVID-19. The possibility of using different administration routes including inhalation and enhancement of MSCs immunomodulatory properties by pre-treatment of MSCs with hypoxia or ischemia provides many attractions for future studies.

Table 1
List of registered MSC-based clinical trials for COVID-19. Abbreviations: I.V.: intravenous infusion; MSCs: mesenchymal stem cells; NA: not applicable.

ID	Phase	Locations	Cell type	Dose	Route
NCT04252118	I	Beijing 302 Hospital	MSCs	3.0×10^7 cells/time (3 times, on Day 0, Day 3, Day 6)	I.V.
NCT04392778	I	Istinye University	MSCs	3.0×10^6 cells/kg (3 times, on Day 0, Day 3, Day 6)	I.V.
	II	Regenerative Medicine and Stem Cell Production Center Liv MedCell Liv Hospital (Ulus)			
NCT04269525	II	ZhiYong Peng, Zhongnan Hospital	UCBMSCs	3.3×10^7 cell/50 ml/bag, 3 bags each time (4 times, on Day 1, Day 3, Day 5, and Day 7)	I.V.
NCT04273646	NA	Huazhong University of Science and Technology, Wuhan, Hubei, China	UCBMSCs	0.5×10^6 cells/kg (4 times, on Day 1, Day 3, Day 5, Day 7)	I.V.
NCT04288102	II	Maternal and Child Hospital of Hubei Province, Wuhan, Hubei, China.	MSCs	4×10^7 cells/time (3 times, on Day 0, Day 3, Day 6)	I.V.
		Wuhan Huoshenshan Hospital, Wuhan, Hubei, China			
NCT04346368	I	Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China	BMMSCs	1×10^6 cells/kg (one time)	I.V.
	II	Nantkwest, Inc.	BM-Allo, MSC	N.A	N.A
NCT04397796	I	Puren Hospital Affiliated to Wuhan University of Science and Technology	UCBMSCs	0.5×10^6 cells/kg (4 times, Day1, Day3, Day5, Day7) suspended in 100 ml saline containing 1% human albumin	I.V.
NCT04293692	NA	Johns Hopkins University	UCMSCs	5×10^5 cells/kg (3 times, Day 1, Day 3 and Day 5)	I.V.
NCT04437823	II	Instituto de Medicina Regenerativa	UCMSC	1×10^8 cells/time (one time)	I.V.
NCT04456361	Early Phase I				
NCT04313322	I	Adeeb Al Zoubi, Stem Cells Arabia	WJMSCs	1×10^6 cells/kg (3 times)	I.V.
NCT04390152	II	BioXcellerator	WJMSCs	50×10^6 cells/time (2 times)	I.V.
NCT04315987	I	Clinical Somer	Conventional treatment plus NestCell*	2×10^7 cells/time (3 times; at Day 1, Day 3 and Day 5)	I.V.
		Azidus Brasil	Dental MSCs	1×10^6 cells/kg (3 times, on Day1, Day 3 and Day 7)	NA
NCT04302519	Early Phase I	CAR-T (Shanghai) Biotechnology Co., Ltd.			
NCT04276987	I	Ruijin Hospital, China	Aerosol of MSCs-derived exosomes	2×10^8 nanovesicles/3 ml at 5 times (Day 1, Day 2, Day 3, Day 4 and Day 5)	Inhalation
NCT04341610	I	JKastrup, Rigshospitalet, Denmark	AMSCs	1×10^8 cells in 100 ml saline	
NCT04331613	II	Qi Zhou, Chinese Academy of Sciences	CASstem	3 cohorts with 3 patients/cohort who receive doses of 3, 5 or 10 million cells/kg	I.V.
NCT04339660	II	Puren Hospital Affiliated to Wuhan University of Science and Technology	UCBMSCs	1×10^6 cells/kg (one time)	I.V.
NCT04336254	I	Renmin Hospital of Wuhan University, China	Allogeneic Human Dental Pulp MSCs	3×10^7 cells/time (3 times, on day 1, day 4 and day 7)	I.V.
NCT04366323	II	Andalusian Network for Design and Translation of Advanced Therapies	AMSCs	8×10^7 cells/time (two times)	I.V.
NCT04349631	II	Hope Biosciences Stem Cell Research Foundation, Texas, United States	Autologous adipose-derived MSCs (AMSCs)	Five times (cell number not applicable)	I.V.
NCT04366063	II	Royan Institute, Tehran, Iran	MSCs	1×10^8 cells with or without extracellular vesicles (EVs) in two times (on Day 0, Day 2 for MSC and on Day 4, Day 6 for EVs)	I.V.
NCT04352803	I	Regeneris Medical	Autologous adipose MSC's (AMSCs)	5×10^5 cells/kg	I.V.
NCT04362189	II	River Oaks Hospital and Clinics	Allogeneic adipose-derived MSCs (AMSCs)	1×10^8 cells/time (4 times on Day 0, Day 3, Day 7, and Day 10.)	I.V.
		Houston, Texas, United States			
NCT04348461	II	Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz	Allogeneic and expanded adipose-derived MSCs (AMSCs)	1.5×10^6 cells/kg (two times)	I.V.
NCT03042143	I	Belfast Health and Social Care Trust, Royal Hospitals	Human umbilical cord-derived CD362 enriched MSCs	Maximum tolerated dose from the phase 1 trial will be infused over 30 to 90 min	NA
NCT04361942	II	Belfast, Northern Ireland, United Kingdom	MSCs	1×10^6 cells/kg (one time)	I.V.
NCT04333368	I	Hospital Universitario Río Hortega Valladolid, Spain	Umbilical cord Wharton's jelly-derived MSCs (UCBMSCs)	1×10^6 cells/kg (three times, Day 1, Day 3 and Day 5)	I.V.
NCT04416139	II	Hôpital Pitié-Salpêtrière – APHP, Paris, France. Hôpital Européen Georges Pompidou – APHP Paris, France	MSC	1×10^6 cells/kg one dose	I.V.
NCT04428801	II	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran Celltex Therapeutics Corporation	Autologous adipose-derived stem cells (AMSCs)	200×10^6 cells/time (three times)	I.V.

(continued on next page)

Table 1 (continued)

ID	Phase	Locations	Cell type	Dose	Route
NCT04348435	II	Hope Biosciences Stem Cell Research Foundation	AMSCs	200 × 10 ⁶ cells/time (5 times, Day 0, Day 2, Day 6, Day 10 and Day 14)	I.V.
NCT04444271	II	Armed Forces Bone Marrow Transplant Center, Rawalpindi, Pakistan	MSC	2 × 10 ⁶ cells/kg (two times, Day 1 and Day7)	I.V.
NCT04429763	II	Fundación Universitaria de Ciencias de la Salud Hospital de San Jose	UCBMSCs	1 × 10 ⁶ cells/kg one dose	NA
NCT04490486	I	Hospital Infantil Universitario de San Jose	UCMSCs	100 × 10 ⁶ cells/time (two times, Day 1 and Day 3)	I.V.
NCT04457609	I	Joshua M Hare, University of Miami	UCMSCs	1 × 10 ⁶ cells/kg	I.V.
NCT04486001	I	Ismael Hadisoebroto Dilogo, Indonesia University VetStem Biopharma, Inc.	PSC-04, (an adipose-derived allogeneic mesenchymal stem cell)	N.A	N.A
NCT04494386	I	Fresno Community Hospital and Medical Center Restern, LLC.	allogeneic Umbilical Cord Lining Stem Cells (ULSC)	100 × 10 ⁶ cells/time (single dose (one infusion) or repeat dose (two infusions separated by 48-h interval))	I.V.
NCT04461925	II	Institute of Cell Therapy Kyiv City Clinical Hospital # 4	Placenta-Derived MMSCs (PMMSC)	1 × 10 ⁶ cells/kg (three times, Day 1, Day 4 and Day)	I.V.
NCT04382547	I	Institute of Biophysics and Cell Engineering of National Academy of Sciences of Belarus	Allogenic pooled olfactory mucosa-derived mesenchymal stem cells	N.A	N.A
IRCT20140528017891N8	III	MOM Research and Innovation Center, Iran (Islamic Republic of)	UCBMSCs	0.5–1 × 10 ⁶ cells/kg (three times, Day 1, Day 3, and Day 6).	NA
IRCT20200325046860N2	I	Baqiatallah University of Medical Sciences, Iran (Islamic Republic of)	MSC	70 × 10 ⁶ cells/time (three times, Day 0, Day 3, Day 6)	I.V.
IRCT20200217046526N1	I/II	Iranian Academic Center for Education culture and research, Iran (Islamic Republic of)	MSC	200 × 10 ⁶ cells/time (three times in Day 0, Day 2, Day 4)	I.V.
IRCT20200413047063N1	I/II	National Institute for Medical Research Development, Iran (Islamic Republic of)	MSC	Three doses of MSCs. Two doses of 100 × 10 ⁶ cells in day 0 and day 2 and day 4.	I.V.
IRCT20190717044241N2	I	Masih Daneshvari Hospital and Shariati Hospital, Iran (Islamic Republic of)	MSC	1 × 10 ⁶ cells/kg (two times)	I.V.
IRCT20140911019125N6	II	Barakat Pharmaceutical Group, Iran (Islamic Republic of Iran) Tehran University of Medical Sciences, Iran (Islamic Republic of Iran) Shariati hospital, Iran (Islamic Republic of), Iran (Islamic Republic of Iran)	Dental pulp mesenchymal stem cells	40 × 10 ⁶ cells/time (one time)	I.V.
IRCT20200418047121N2	I/II	Alzalipour Hospital and Stem Cell and Regenerative Medicine Comprehensive Center of Kerman University of Medical Sciences, Iran (Islamic Republic of Iran) Kermanshah University of Medical Sciences, Iran (Islamic Republic of Iran)	MSC	1 × 10 ⁶ cells/kg (three times, every 3–4 days during a 14-day period)	NA



Fig. 2. The diagram depicts the challenges and considerations of MSCs-based therapy.

CRedit authorship contribution statement

Somaye Sadeghi: Investigation, Writing - original draft, Writing - review & editing, Validation. **Sara Soudi:** Investigation, Writing - review & editing, Validation. **Abbas Shafiee:** Conceptualization, Writing - review & editing, Validation. **Seyed Mahmoud Hashemi:** Conceptualization, Writing - review & editing, Validation.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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