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Cell Therapy as an Alternative approach for COVID-19 Infection Consequences: A Non-Systematic Review

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Abstract

The current uncontrollable outbreak of novel coronavirus (COVID-19) has unleashed severe global consequences in all aspects of life and society, bringing the whole world to a complete halt and has modeled significant threats to the global economy. The COVID-19 infection manifests with flu-like symptoms such as cough, cold, and fever resulting in acute respiratory distress syndrome (ARDS), lung dysfunction, and other systemic complications in critical patients are creating panic across the globe. However, the licensed vaccine has started to show up; some resulted in side effects that would limit its possibility in some circumstances as allergic personnel, for example. Moreover, the production and approval of new drugs is a very complicated process and takes a long time. On the other hand, stem cells have gone the extra mile and intensively investigated at preclinical and clinical studies in various degenerative diseases, including infectious ones. Stem cells are proposed as a broad-spectrum therapeutic agent, which may suppress the exaggerated immune response and promote endogenous repair by enhancing COVID-19 infected lung microenvironment. Also, stem cells have different application manners, either direct transplantation, exosome transplantation, or drug delivery of specific cytokines or nanoparticles with antiviral property by engineering stem cells. This review discusses and summarizes the possible emerging role of cell-based therapy, especially stem cell therapy, as an alternative promising therapeutic option for the treatment and control of novel COVID-19 and its potential role in tissue rejuvenation after COVID-19 infection.

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Introduction

The recent uncontrollable outbreak of novel coronavirus (COVID-19) infection is wreaking havoc in several countries. COVID-19 has first reported in Wuhan State of Hubei Province in China, is now a severe novel threat to public health with the emergence world over [1]. On Dec. 12, 2019, the first patient of pneumonia was observed in Wuhan, China. After then cluster cases of severe pneumonia epidemic of unknown origin were again recorded in Wuhan city, China. At the end of December 2019, these cases have quickly been transmitted in China and many other countries worldwide [2]. On Mar. 11, 2020, The World Health Organization (WHO) has declared; COVID-19 is a pandemic and has modeled severe public health threats and the global economy [3, 4].

The COVID-19 disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), an aggressive strain and highly infectious pathogen that mainly targets the human upper respiratory system [5, 6]. Genomic sequence data of SARS-COV-2 revealed that COVID-19 is highly similar to bat SARS-like coronavirus (bat CoV RaTG13) (96.2%) and pangolin SARS-like coronavirus (86%-92%). Based on these analyses, bats could be the possible primary host for this virus [7-9]. To date, there is doubt about the efficacy of approved vaccine. Therefore, there is an extremely urgent global priority to identify therapeutic options as soon as possible to prevent and control the pandemic. Due to the lack of effective and specific treatment regimen against novel coronavirus and considering the potential menace of this pandemic, researchers have been battling to understand the molecular biology of this novel strain and disease pathophysiology to uncover valuable therapeutic modalities and discover effective drug treatment against the virus.

In the meantime, there is a superhero therapeutic compartment that has proven to be efficient in a wide range of degenerative diseases, which is stem cells. It also raised as an alternative therapeutic agent because till now; there is no logical explanation of why some patients are more drastically affected by COVID-19 infection. However, the majority would recover very fast. We do believe that endogenous stem cells may play a role in such different responses.

Since COVID-19 infection is mainly detected in the upper and lower respiratory tracts but not in the spleen, bone marrow, lymph nodes, and heart. Patients with COVID-19 infection showed various significant clinicopathological changes in their lower respiratory tract, immune organs, and systemic blood vessels, emphasizing that viral infection may modulate and over-activate immune responses in the human body. However, immune modulation approaches might be potentially helpful to improve antiviral immunity and reduce the viral load, enhance outcomes and recovery of COVID-19 patients. In this regard, stem cell-based therapy is a novel emerging potential intervention that may help inhibit the overreaction of immune response and promote endogenous repair by enhancing the SARS-COV-2 infected lung microenvironment. This review discusses and summarizes the possible emerging role of stem cell therapy as an alternative therapeutic option for the treatment and control of novel COVID-19.

Methods/Source of Data

We searched the relevant published literature on PubMed, Embase, Google Scholar, Medline, Science Direct, WHO and disease Control and Prevention (CDC) online publication databases and was selected using the following keywords and phrases Stem cells, engineered stem cells, Exosome, Lung fibrosis, Lung regeneration, COVID-19 and SARS-COV-1 and 2. A literature search was conducted from April 2020. We also used the following website to retrieve the registered clinical trials (https://www.clinicaltrials.gov/). Literature type include online published international peer-reviewed articles, commentaries, online reports, editorials and electronic books for this review article.

Results

Novel COVID-19 Pathogenesis and Clinical Presentation

Novel coronavirus (corona = crown-like spikes) small enveloped, positive-sense single-stranded RNA (+ssRNA) virus belongs to the family Coronaviridae. The virus is transmitted predominantly through direct close contact with an infected person; small respiratory droplets and aerosolization/fecal-oral route are also strongly possible. Infection is more contagious when patients are symptomatic, but it can also be transmitted with asymptomatic patients' close contact and before symptoms appear [10]. The infected droplets of COVID-19 can transfer up to 1-2 meters. The novel

coronavirus can survive for up to 3 hours in aerosols and 72 hours on hard and nonporous surfaces [11]. The onset of SARS-CoV-2 symptoms appears in 5.2 days, with a median incubation period of 14 days**.** The incubation time is dependent on various factors such as the patient's age, immunity, and history of acute and chronic diseases, but 97.5% of patients can develop symptoms in 11.5 days after infection [12]**.** COVID-19 infection is susceptible to all ages, but the vulnerable population is more sensitive.

Patients with chronic diseases (diabetes, asthma, cardiovascular disease, kidney failure, obesity, malignancy, etc.) and older individuals have an increased risk of disease severity and fatality. Recent studies have identified human angiotensin-converting enzyme 2 (ACE2) as a crucial receptor for the SARS-CoV -2 and can enter the host cell's respiratory mucosa through the ACE2 receptor [13, 14]. ACE2 enzyme is the most abundant enzyme in the lung's alveolar cells and is expressed in the nasal mucosa, esophagus, bronchus, gastrointestinal tract, kidney, ileum, and bladder. Viral replication primarily occurs in the upper respiratory tract's mucosal epithelium and later, with further multiplication, causes a severe lower respiratory tract infection [15]. It has been identified recently that coronavirus spike protein (glycoprotein) has a strong binding affinity to human ACE2 receptor, and both SARS-COV and SARS-COV-2 spike proteins have a high degree of homology and share 76.5% identity in amino acid sequences [14, 16]. The spike proteins of SARS-COV and SARS-COV-2 viruses help the attachment and entry of the virus into the host cells (Fig. 1). It has suggested that attachment of the SARS-CoV-2 spike protein to the ACE-2 receptor and the complex transmembrane protease, serine 2 (TMPRSS2- crucial for entry of virus) on the surface of the cell membrane leading to cleavage of ACE2 receptor and open the spike protein, therefore, enabling viral entry into the target cell. After entry of the virus, the viral ssRNA unveiled in the host cell. After the virus enters the host cell, the viral genome is transcribed, and viral proteins are synthesized. After ACE2 receptor binding and fusion,

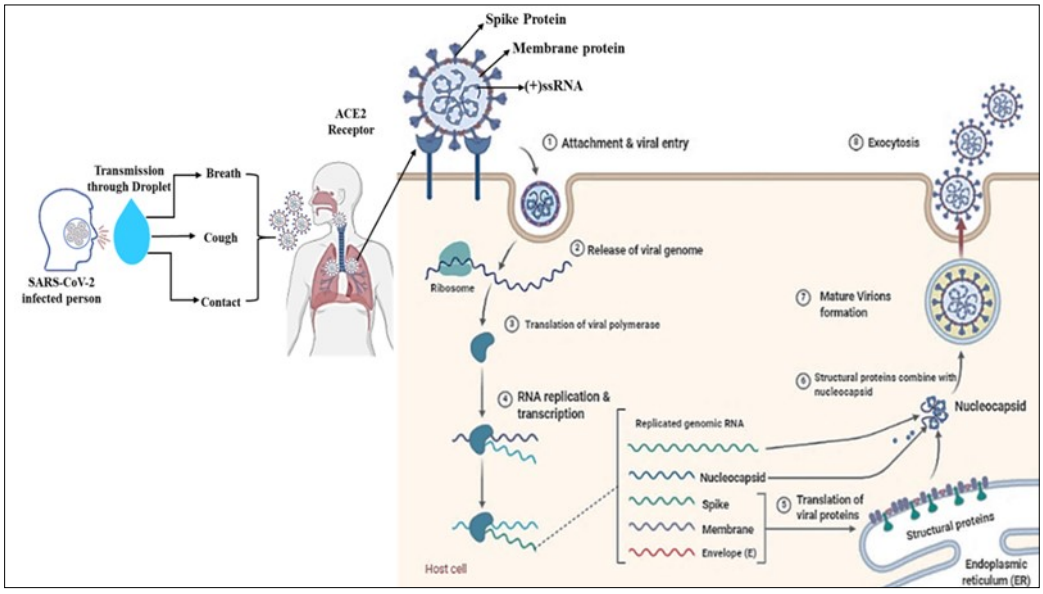

Figure 1. SARS-CoV-2 transmission, entry life cycle in host cells. Spike (S) proteins of SARS-CoV-2 are attached to receptors (ACE2) on the target cell membrane's surface through the endosomal pathway. After entry of the virus, the viral ssRNA unveiled in the host cell. After ACE2 receptor binding and fusion, virus-specific RNA and proteins are synthesized in the cytoplasm. After the virus's entry into the host cell, the viral genome is transcribed, and viral proteins are synthesized. Viral nucleocapsids, assembled at the cell membrane and genomic RNA, are incorporated as mature particle forms by budding into the endoplasmic reticulum's lumen. The mature virions are then released through the exocytosis process.

virus-specific RNA and proteins are synthesized in the cytoplasm. Viral nucleocapsids assembled at the cell membrane, and genomic RNA in the cytoplasm is incorporated as the mature particle forms by budding into the lumen of the endoplasmic reticulum [17, 18].

The mature virions release genetic material into the cell, imposing the cell to make copies of the virus that are transmitted to infect other cells (Fig. 1).

Initially, the majority of COVID-19^{+ve} patients either asymptomatic or showed usual flu-like symptoms such as temperature (98%), dry cough (76%), dyspnoea (55%), and fatigue (44%). Remarkably, few patients faced difficulty breathing, chest pain, difficulty walking, weakness, reduced lymphocyte counts, and other uncommon clinical features like runny nose, sore throat, nasal congestion, sputum production, headache, vomiting, dyspnoea, diarrhea, and anosmia [19]**.** The global case fatality rate (CFR) across all communities is about 4.9% [20].

Mesenchymal Stem Cells (MSCs)

MSCs are naïve cells with no identity but can differentiate into more specialized cells such as cartilage and bone cells [21]. As defined by the "International Society of Cell Therapy (ISCT)," MSCs should meet specific criteria to be considered as real stem cells [22]. These criteria are 1- the ability to adhere to plastics with fibroblastic shape, 2- positively express specific surface markers as "CD105, CD73 and CD90" but not "CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR" and 3- capable of differentiating into bone cell "osteoblast", fat cell "adipocyte" and cartilage cell "chondrocyte" in the presence of appropriate growth factors for each cell line [23].

MSCs have proven to restore lung function in various viral affections shares the same symptoms with COVID-19. For instance, BMSCs have been demonstrated to efficiently promote rehabilitation, survival rates and mitigate the inflammatory response in animal models infected with influenza A H1N1, H5N1, and H9N2 avian influenza [24-26]. Also, Umbilical cord mesenchymal stem cells (UCMSCs) restored alveolar fluid clearance and membrane permeability after influenza A virus H5N1 [27]

Similarly, stem cells strongly proposed to be involved in the treatment protocol strategy of COVID-19. They have a high potential to modulate the immune system (decrease the hyperimmune activity) and stimulate the damaged tissues' regenerative process, hence accelerating recovery. Moreover, Stem cells isolated from the umbilical cord, adipose tissue, and placenta have been proven resistant to SARS-Cov-2 infection as confirmed by low ACE2 expression [28].

Additionally, stem cells have been demonstrated to shed tiny fragments at a nano-size range named later as exosomes. These particles are composed of a phospholipid membrane, which envelops proteins, cytokines, and genetic messengers. The function of released exosomes is mainly to help stem cells to work remotely at peripheral sites in the body by delivering their regenerative cues.

At the clinical application, exosomes are believed to be more advantageous as a therapeutic agent than stem cells. It will fulfill the demanded regenerative effect entirely similar to their parent cells. Moreover, exosomes provide hope for easy, safe, affordable, and off-the-shelf biological therapy [29-33]. Also, it is worth to mention that exosome derived from MSCs (EX-MSCs) has tested for its protection as well as therapeutic potential in some viral diseases as Hepatitis C Virus (HCV), Herpes Virus (HSV), and influenza virus at in vitro and in vivo [34-36]. Moreover, exosomes can play a significant role in rejuvenating degenerated lung tissues, secondary to SARS-CoV-2, as it possesses antioxidant, antifibrotic, anti-inflammatory, anti-apoptotic, matrix integrity, and other regeneration cues [37].

The Expected Outcome from Stem Cells and its Derivatives Transplantation to COVID 19 Patients

Treatment of viral disease could be approached by either preventing the virus from entering the cells, restrict virus survival and replication in the hosting cells, and inhibit excessive host immune response [38].

Many studies consensus that stem cells harbor a potential antiviral effect against polyomavirus, influenza A, and cytomegalovirus [27, 39, 40]. Moreover, Stem cells have a strong regenerative and therapeutic effect as they can produce cytokines capable of stimulating cell proliferation and differentiation, enhancing vascularization, and reducing fibrosis (Fig. 2).

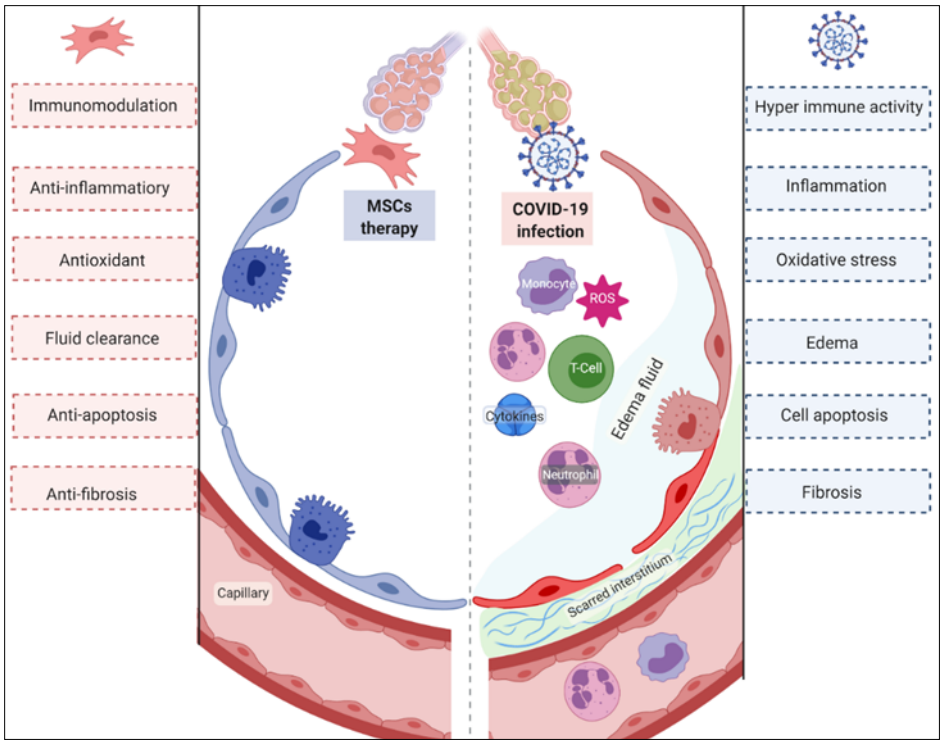

Figure 2. The expected outcome from stem cells and its derivatives transplantation to COVID 19 patients.

Homing

Although stem cells can migrate to the site of injury in various organs upon intravenous (IV) transplantation, there is a piece of high evidence that stem cells got entrapped in the lung after IV transplantation [41, 42]. This spontaneous homing capacity of stem cells to the lung will significantly benefit the lung regeneration procedure. It's also worth mentioning that entrapment of MSCs in the lung resulted in its activation and enhanced the secretion of TSG-6 (anti-inflammatory protein) [43].

Antiviral Effect

Swartzendruber and his group showed that the pluripotent stem cells exhibit antiviral potential and suppress polyomavirus function counter to differentiated somatic cells, which were more susceptible to the infection [39, 44]. This finding proposed that stem cells may possess a defense mechanism by which it can degrade the foreign DNA [39]. A lot of studies have conducted to prove the efficacy of MSCs and their derivatives as therapeutic agents in viral infections from then onwards.

UCMSCs have been demonstrated to restore the alveolar epithelial cells permeability and alveolar fluid clearance related to Influenza A (H5N1) virus infection in the rat animal model [27]. Also, BMSCs-conditioned media has shown productive antiviral activity against HSV in vitro as it contains IL-6 and TNF-α [36]. This finding confirmed by an in vivo study in which BMSCs injection resulted in a 70% survival rate compared to 10% in the control group. These results attributed to the ability of BMSCs to activate T cell proliferation, reduce the pro-inflammatory cytokines IL-6 and TNF-α, and enhance INF-γ production.

Similarly, EX-MSCs can provide a potential antiviral function. For instance, EX-UCMSCs have been demonstrated to suppress HCV replication in vitro [34]. This antiviral effect is attributed to a specific miRNA mixture (let-7f, miR-145, miR-199a, and miR-221) released by EX-UCMSCs. This finding suggests the EX-UCMSCs as an optimal adjuvant of anti-HCV therapy. Furthermore, extracellular vesicles derived from swine BMSCs (EV-BMSCs) exhibited anti-influenza viral activity in vitro by inhibiting the virus replication and reducing the virus-related lung epithelial cells apoptotic effect [35]. At the *in vivo* pig model, intra-tracheal administration of EV-BMSCs could successfully provide antiviral and anti-inflammatory effects that alleviate the

influenza virus (H1N1) related lung lesions.

Immunomodulatory and Anti-Inflammatory Effect

It has demonstrated that the high fatality rate of COVID-19 hails from the acute hyper-immune response from the lung immune system (or hyperactivity of the lung immune system); this phenomenon is known as ARDS [45, 46].

In 2015, two patients suffering from ARDS succumbed BMSCs transplantation. The treatment was very efficient in resolving the inflammation and suppressing T-cell responses, and induction of regulatory phenotypes in T cells, monocytes, and neutrophils [47]. Similarly, after allergic asthma, the regeneration of lung tissues was also obtained after intra-tracheal administration of BMSCs in mice model.

Since the administration of IFN-α was influential in the treatment of COVID-19 patients and resulted in a high viral mRNA elimination rate [48], engineered stem cells designed to deliver INF-α may provide a successful strategy in the treatment of COVID-19. IFN-α-engineered MSCs has tested before for its efficacy to control tumor in a mouse "plasmacytoma model" [49] and acute myeloid leukemia [50].

EX-MSCs have shown the same anti-inflammatory and immunological response as their parent cells. For example, EX-ADSCs were reported to reduce IFN-γ, consequently inhibiting T cell activation and induced macrophage polarization [51, 52]. Recently, exosomes derived from placenta MSCs (EX-PLMSCs) predominantly reduced TNF-α, IL-1β, IL-12, and IFN-γ inflammatory cytokines and increased the level of IL-10 immunosuppressive cytokine; hence it resulted in suppressing inflammation [53].

Modulation of Lung Fibrosis and Endothelial Barrier Permeability

Lung fibrosis is one of the most severe complications of COVID-19. Fibrosis results in tissue thickening (as confirmed by histopathological examination), which hinders gas exchange and hence lower blood oxygen tension in which patients manifest ARDS symptoms [54, 55]. Stem cells and their derivatives have provided an innovative therapeutic approach to resolve the associated COVID-19 lung fibrosis.

Intravenous injection of UC-MSCs and BMSCs have been shown to effectively ameliorate lung fibrosis in different animal models [56][57]. Moreover, stem cells and their conditioning media exhibited a high potential to enhance the endothelial barrier permeability and restore the alveolar fluid clearance capacity (which was disturbed by E. coli endotoxin) through keratinocyte growth factor (KGF) [58]. Interestingly, intrapulmonary administration of BMSCs had a similar effect in that it could restore the alveolar permeability and reduce pulmonary edema [59]. Moreover, Asmussen et al. added that MSCs dose plays an essential role in the clinical output. A dose of 10×10^6 BMSCs/kg reduced the pulmonary edema more efficiently than 5×10^6 cells/kg in the E. coli pneumonia sheep model [60].

In order to enhance the alveolar epithelial cell regeneration, which eventually will impact pulmonary permeability dominance, Zhang et al. have proposed to engineer BMSCs to overexpress p130 or E2F4 [61]. The results of this study revealed that p130/E2F4 could inhibit lung fibrosis, promote MSCs differentiation into epithelial cells, and hence enhanced alveolar epithelial permeability.

ACE2 has been reported to prevent lung injury resulting from septicemia, acid inhalation, or endotoxin shock [62]. Also, it showed a protective effect on pulmonary endothelial cells from apoptosis in vivo and in vitro [63]. The exploitation of stem cells to deliver the ACE2 gene in what is known as engineered stem cells has been proposed to treat lung injury effectively. For example, ACE2 engineered UC-MSCs significantly alleviated inflammation, fibrosis, and pulmonary permeability [64, 65]. It also has shown a protective effect on DNA damage and possesses antioxidant property [66, 67]. Likewise, ACE2 engineered BMSCs manifested an anti-inflammatory effect and improved the pulmonary endothelial function [66].

Applying this hypothesis based on the preclinical findings in Corona virus-infected patients may be tricky and not guaranteed. The reason lies in the possibility of ACE2-cells to get infected with CoV-19, similar to SARS-2003 [68-70]. These last findings spur Whuan medical staff to use $ACE2^{-ve}$ MSCs in their treatment protocol strategy in Beijing YouAn Hospital [71].

Anti-Apoptotic and Antioxidant Effect

Stem cells have a potential role in preventing cell death. For instance, BMSCs has shown a significant

effect on Isoproterenol-induced lung injury (ISP-LI) as it reduced the caspase-3 activity and upregulated nuclear-related factor-2 (Nrf2, antioxidant marker) [72].

EX-ADSCs exhibit a protective effect on cardiomyocytes against reactive oxygen species (ROS), which has a drastic impact on cell viability [73]. In terms of the engineering of stem cells to meet specific criteria as alleviating apoptosis, exosomes derived from GATA-4 engineered MSCs have proven to protect cells in damaged tissues upon its transplantation and increase survival rate [74]. Furthermore, EX-BMSCs could alleviate lung ischemia by delivering "MiR-21-5p" anti-apoptotic miRNA and protecting cells from oxidative stress [75].

MSCs also were reported to have a potent antioxidant effect. BMSCs reported reducing ROS production in HCL injured lung animal model through upregulation of antioxidant enzyme Hemeoxygenase-1 (HO-1) [76]. Interestingly, apoptotic ADSCs (serum-deprived cells) have been shown to produce a superior antioxidant protective effect on lung and kidney injury than healthy ones [77]. This effect was attributed to high antioxidant protein expression as HO-1, glucocorticoid (GR), and NAD(P)H dehydrogenase (NQO-1). Also, EX-UCMSCs exhibited a protective antioxidant effect on UV-treated cells as detected by high antioxidant proteins, "glutathione peroxidase 1 (GPX-1), superoxide dismutase (SOD), and catalase", expression [78].

Clinical Trials

In terms of testing stem cells efficacy from various sources (including BMSCs, ADSCs, Decidual stromal cells, Menstrual blood stem cells, and HUCMSCs) as a therapeutic agent for ARDS, which is the primary symptom of COVID-19, there were about 11 clinical trials have been registered from 2013 to 2020.

Some clinical trials has shown that stem cells are safe, tolerable, and effective in alleviating ARDS related symptoms as shown in Table 1. Currently nine clinical trials registered, aiming to investigate stem cells' efficacy in the COVID-19 treatment strategy. Most of these trials from China, one from Brazil, and one from Amman.

UC-MSCs were used successfully to treat one COVID-19 positive female patient (65-years old) in which she received three doses; each one was $50*10^6$ every three days [62]. Another clinical trial included seven patients diagnosed as COVID-19 to be treated with $ACE2^{-ve}$-MSCs transplantation [71]. The results of this study revealed that $ACE2^{-ve}$-MSCs transplantation has significantly improved pulmonary function as well as increased the peripheral lymphocyte and IL-10 cytokines.

EX-MSCs have been previously tested for their potential to treat lung-related diseases as a chronic obstructive pulmonary disease (COPD) [53, 79], Asthma [80], lung fibrosis [81, 82], and ARDS [83]. These studies confirmed a high potential of exosomes to reduce inflammation and contribute to tissue remodeling. Consequently, these optimistic outputs boost their incorporation in clinical trials. Recently, a

Table 1. Some Clinical Trials of various sources of stem cells as a therapeutic agent for ARDS.

Trials	Methodology	Results	Ref
Allogeneic ADSCs ($1*10^6$ cell/kg)	12 ARDS	The treatment was safe and tolerable; but non-significant to the placebo group.	(104)
BMSCs ($10*10^6$ per kg)	9 ARDS	Resulted in significantly higher clinical output. The mortality rate was 22% (other reasons than treatment protocol).	(105)
UC-MSCs	9 ARDS	Reduced the inflammatory biomarkers and increased the immune T-cell markers (helper, cytotoxic, and regulatory T-cell)	(106)

clinical trial proposed to use EX-ADSCs through inhalation for the treatment of pneumonia-related COVID-19 infection (NCT04276987). Two completed studies associated with EX-MSCs and Covid-19 have been conducted in China (NCT04276987) and Russia (NCT04491240). Exosomes inhalation can diminish lung tissue inflammation and promote tissue regeneration by boosting the immune cells and promote tissue regeneration. They also validate that exosome inhalation is a safe and productive treatment [1].

Precautions of Stem Cells Transplantation

In terms of precautions that should be considered in stem cell therapy, there will be three aspects, the first aspect related to donors, the second related to cell therapy preparation, and the final one associated with patients (therapy recipients).

Donors should be screened thoroughly. Selection of the donors should be subject to some considerations as the donor age and health status as they have proven to impact the stem cells quality and the derived exosomes.

Cell therapy preparation: High precautions should be taken to prevent contaminations. Also, cells should go through many investigations to prove their viability, efficacy, and safety. Taken into consideration, the raised warnings from using an unproven stem cell therapy instead of properly tested ones are the physician's primary responsibility, as discussed by [84, 85]. Furthermore, the cell expansion status (whether 2D or 3D culture) is dramatically affecting the stem cells quality, so reporting this piece of information in the medical report will significantly enhance the evaluation of the therapeutic efficacy and future trials [86, 87].

Recipients should be checked if they have a cancer history. Stem cell therapy may worsen cancer patients' health status as proved in vitro and in vivo studies [88]. In this regard, we highly recommend using engineered MSCs or their derivatives exosomes because some of the patients may have subclinical cancer or tumors; this will open the door for more trustable, controllable, and safe therapeutic agents [89, 90]. The administration route should be through IV as it has demonstrated that stem cells got entrapped in the lung in IV administration [91]. Moreover, as reported by Atluri, Manchikanti [92], monitoring the patients during the therapy transplantation is very important to prevent organ embolization and allergic reactions. Also, as it is well known that MSCs compared to controls were associated with an increased risk of fever, controlling the body temperature is of high demand [93].

Future Directions to Control COVID-19 Transmission.

Herein, we shed light on the possible therapeutic potential effect of stem cell therapy and its derivatives on COVID-19. We will also highlight the possibility of involving genetic engineering and nanotechnology to enhance stem cells' regenerative capacity and their derivatives (Fig. 3).

As shown in recent studies and clinical trials that incorporated stem cell therapy in the treatment protocol of some viral infection cases and COVID-19, in particular, that stem cells have a high potential to modulate the immune response and regenerate tissues. Herein, we propose a couple of ways to enhance the stem cell's therapeutic efficiency and increasing its potential. That can be accomplished by either genetic engineering of stem cells or NPs engineering. MSCs genetic engineering can be achieved by either upregulation of specific genes (which are necessary for the regeneration process) or downregulation of other genes (which may be involved in the virus virulence) [94]. Engineered MSCs have proven high potential to control tumors, provide high vascularization, attenuate inflammation, and act as a vaccine by providing immune protection against some viruses [49, 95-97].

In addition, stem cells are proposed as an excellent mediator to deliver NPs with antiviral properties since they possess a high affinity to migrate into the lung. The nanotechnology field advances lead to inducing nanoparticles (NPs) modifications to accommodate the viral infection control strategy. For instance, some NPs as Rheum tanguticum, tannic acid-modified silver (TA-Ag), polyethylene glycol coated zinc oxide (ZnO-PEG), and Gold/Copper Sulfide (Au/CuS) have shown to be effective against Herpes simplex virus type 1 (HSV-1), HSV-2, influenza virus (H1N1), and Human norovirus respectively [98-101].

To get a closer idea about the effect of NPs on the currently pandemic SARS-2 infection, we will spot the light on a couple of NPs that have been modified and tested on viruses from the same family

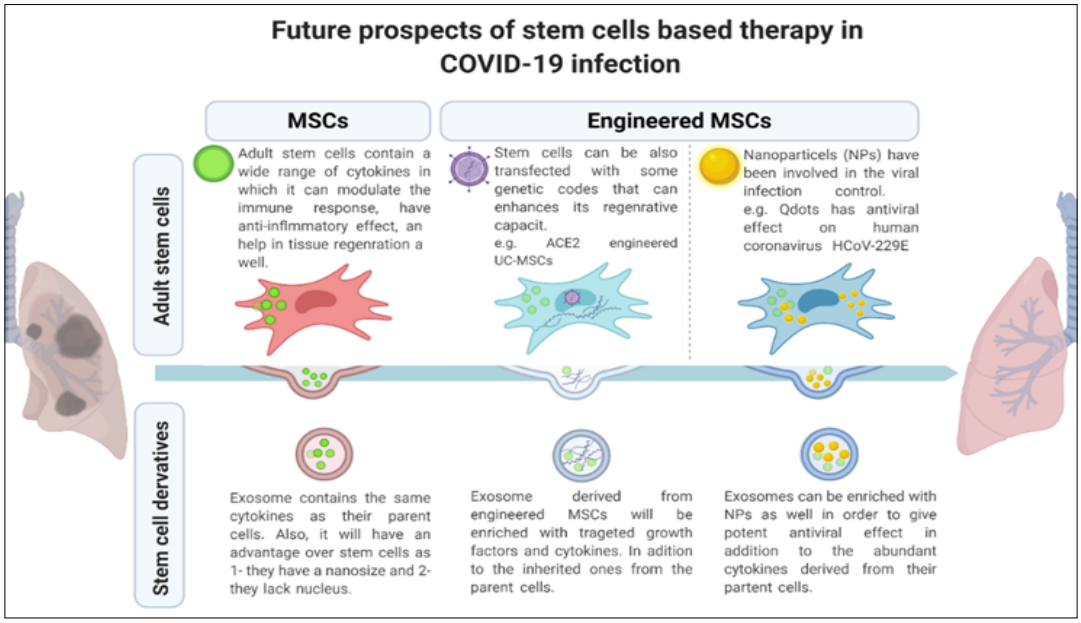

Figure 3. Future directions to control COVID-19 transmission. 1- Adult stem cells (the upper raw), including MSCs, have proved to be effective in promoting the recovery of COVID-19 patients. Also, as per the available data, we propose engineering MSCs either by genetic engineering in which we can direct MSCs to produce specific growth factors or loading MSCs with NPs (known to have an antiviral capacity). 2- Exosome (the lower raw), since exosome proved to have similar potential as their parent cells. Then exosomes derived from the naïve MSCs, genetically engineered MSCs, or NPs engineered MSCs can be involved in the therapeutic protocol as well with higher efficiency.

(Coronavirus). The antiviral activity of Qdots has been investigated on human coronavirus HCoV-229E in which Qdots cause inhibition of the virus at the entry stage and replication stage due to the capacity of the NPs to interact with the virus entry receptors [102]. Another example is using gold NPs against Middle East respiratory syndrome coronavirus (MERS-CoV) [103]. In this study, authors could raise the peptide pregnancy-induced hypertension (PIH, peptide has an inhibitory effect on MERS-CoV membrane fusion to host cells) potential 10-fold by its integration with gold NPs. In the same manner, NPs can be used to target the SARS-2 virus as well.

As explained earlier, exosomes can supersede stem cells efficiently and beat on the raised issues against their use. Exosomes derived from the previously mentioned engineered MSCs can also enhance their regenerative capacity and increase the successful cure rate. Moreover, the possibility of being administered by inhalation can decrease the overload of hospitals.

In conclusion, with the absence of specific and effective antiviral treatment against novel coronavirus, stem cells and their derivatives exosomes are our great hope and efficient promising tools as antiviral agents for treating COVID-19 patients. These emerging approaches might improve critically ill pneumonia patients' outcomes through anti-inflammatory, anti-immunomodulatory actions, and promoting tissue repair and recovery.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethical Approval

Not applicable

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