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Review Article

Mesenchymal stem cell alongside exosomes as a novel cell-based therapy for COVID-19: A review study

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ABSTRACT

In the past year, an emerging disease called Coronavirus disease 2019 (COVID-19), caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been discovered in Wuhan, China, which has become a worrying pandemic and has challenged the world health system and economy. SARS-CoV-2 enters the host cell through a specific receptor (Angiotensin-converting enzyme 2) expressed on epithelial cells of various tissues. The virus, by inducing cell apoptosis and production of pro-inflammatory cytokines, generates as cytokine storm, which is the major cause of mortality in the patients. This type of response, along with responses by other immune cell, such as alveolar macrophages and neutrophils causes extensive damage to infected tissue. Newly, a novel cell-based therapy by Mesenchymal stem cell (MSC) as well as by their exosomes has been developed for treatment of COVID-19 that yielded promising outcomes. In this review study, we discuss the characteristics and benefits of MSCs therapy as well as MSC-secreted exosome therapy in treatment of COVID-19 patients.

1. Introduction

Coronaviruses are positive single-strand RNA viruses with a size between 60 nm to 140 nm that predominantly hold spike-shape protein as the major ligand for host cell entry [1]. Four strains of coronaviruses, including NL63, 229E, OC43, and HKU1 have been prevalent among the population, and cause gentle respiratory disease. Two evidences have been documented so far in the past 20 years demonstrating that transmission of animal β coronaviruses to humans has been occurred during the intense disease. The first case of this was in 2002, when the new β coronavirus, a bat-driven coronavirus, was transmitted to humans through a host-mediated route by palm cats in China's Guangdong Province. In 2012, an unknown sickness named the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) with bat origin, emerged in Saudi Arabia which dromedary camel was its intermediate host and infected 2494 people and caused 858 deaths cases [2,3]. In Wuhan, pneumonia morbidity of an unknown source was announced in December 2019. In January 2020, a new type of coronavirus, entitled severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified [4,5]. World Health Organization (WHO) denominated pandemic infection as coronavirus disease 2019 (COVID-19) in February 2020. Since then, SARS-CoV-2 has been spreader in more than 200

Abbreviations: COVID-19, Coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; MSC, Mesenchymal stem cell; MERS-CoV, Middle East Respiratory Syndrome Coronavirus; ARDS, Acute respiratory distress syndrome; ACE2, Angiotensin-converting enzyme 2; CXCL10, C-X-C motif chemokine ligand 10; HGF, Hepatocyte growth factor; TMPRSS2, Transmembrane protease/serine2; RAS, The Renin-Angiotensin system; MIP1α, macrophage inflammatory protein 1α; MCP1, monocyte chemoattractant protein 1; TNF, tumor necrosis factor; DCs, dendritic cells; HLA, human leukocyte antigen; KGF, Keratinocyte growth factor; IL-1RA, Interleukin-1 receptor antagonist; MMP, matrix-metalloprotein; VGEF, Vascular endothelial growth factor; VE, Vascular endothelial; AAT, Alpha-1-anti trypsin; TGF, Transforming growth factor.

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countries that has led to recession and social constraints in society also has posed many challenges to the health care system.

The average incubation period in some patients is long, ranging from 2 to 14 days [6,7]. Some infected individuals show very mild symptoms and even be asymptomatic, while the elderly and people with chronic diseases like diabetes and lung disease develop more severe symptoms that can lead to acute respiratory distress syndrome (ARDS) and multiple failures of limbs with a high mortality rate. Currently, there is no effective drug to treat COVID-19 patients that has challenged its control and management [8–12]. A new clinical study just published by Zhao and coworkers in the journal Aging & Disease indicates that intravenous prescription of human mesenchymal stem cells (MSC) in seven patients with confirmed COVID-19 improved functional outcomes [13]. In this article, we discuss the remedial potential of MSCs and their exosomes for treatment of COVID-19 cases.

2. Pathogenesis of COVID-19

According to the cells which are presumably infected, SARS-CoV-2 can be considered through three stages of sickness that corresponding to the different clinical phase of the disease, including asymptomatic state (stage 1), upper airway and response (stage 2) as well as hypoxia, ground-glass infiltrates, and advancement to ARDS (stage 3) [14].

2.1. Stage 1

When the virus enters the body through the nasal cavity, it attaches to the epithelial cells through its surface ligands and begins to replicate. Angiotensin-converting enzyme 2 (ACE2) is the major receptor for Spike protein at the surface of SARS-CoV2 and SARS-CoV. In vitro studies revealed that the ciliated cells are the first type of cells infected in the respiratory tract by SARS-CoV [15,16]. After that, the virus spreads locally, to which the immune system's response is limited. At this stage, the coronavirus can be isolated by a nasal swab. Although the number of virus particles may be low, infected individuals can transmit the virus to others as carriers of the virus. The RT-PCR test with standard sample collection procedure is very valuable for detecting carrier subjects. In addition, determining the load of the virus is also helpful in predicting clinical conditions [17].

2.2. Stage 2

At this stage, the burden of viruses increases and it migrates through the conductive airways to the lower parts of the lungs followed by a stronger innate immune response. At this time, clinical manifestations of the disease appear, including fever, dry cough, tiredness, sore throat, diarrhea, loss of tasting or smelling senses, headache, and systemic body pains. The innate immune system mediators, such as C-X-C motif chemokine ligand 10 (CXCL10) may help to predict the next clinical stage of COVID-19. Coronavirus infected epithelial cells are the primary provenance of β and λ interferon production [18,19]. In a recent study, to evaluate the feasibility of identifying biomarker factors for disease intensity and development of COVID-19, Yang and colleagues illustrated that among the large part of circulating cytokines in individuals with COVID-19, 14 were significantly elevated as compared to healthy controls group.

Besides, researchers have shown that CXCL10, CXCL9, CCL7, CCL3, and Hepatocyte growth factor (HGF) expression levels can be significantly associated with disease severity [20]. Hopefully, about 80% of people with the virus have mild symptoms and the infection is limited to the upper respiratory tract. It is recommended that these people rest at home and be monitored to break the chain of transmission of the virus to others [14].

2.3. Stage 3

Unfortunately, in 20% of cases with COVID-19, disease enter to stage 3, in which the respiratory system is completely damaged by the virus and the disease worsens. Investigations show that the mortality rate is about 2%, which is significantly related to the patient's conditions and risk factors like age [14]. The virus migrates to the gas exchange parts of the lung and affects alveolar type II cells. Both influenza and SARS-CoV are more likely to infect alveolar type II cells than type I cells [21]. Following the multiplication of the coronavirus in type II cells, a large number of viral structures are released and the cells undergo apoptosis [22]. The pathological complication of the virus results in extensive alveolar tissue damage replaced by a fibrin-rich hyaline membrane and giant multinucleated cells [23].

Elderly infected patients are at exceptional risk due to a compromised immune response and diminished ability to repair damaged epithelium. Another noteworthy point is the reduced mucociliary clearance ability in the elderly patients that allows the virus spread and settle in the oxygen exchange parts of the lungs more readily [24].

2.4. Blood clots in SARS-CoV-2

The SARS-CoV-2 can induce vascular damage. Afterwards, the circulating platelets are exposed to collagen and endothelium, and become the active platelet form. Activated platelets release the essential factors, including adenosine diphosphate, serotonin, thromboxane A2, and prothrombin to further activate platelets. On the other hand, 12 coagulation factors are needed to start the clotting process in the arteries. Briefly, the factor XII activated and lead to prothrombin conversion to thrombin. Finally, fibrinogen convert to fibrin which constitute a network of fibrins at the damaged area to clot blood. In addition, several important and dangerous coagulation complications such as disseminated intravascular coagulation, pulmonary embolism, and venous thromboembolism can be caused by the virus and make the treatment of patients more challenging [25].

3. SARS-CoV-2 and immune system

Only recently at December 2020 effective vaccines have been developed to immunize patients with COVID-19. However, the immune system can be effective as the body's natural response to pathogens and infections [26]. SARS-CoV-2 uses the ACE2 as a receptor to attach to host cells, including airway epithelial cells. Transmembrane protease/serine2 (TMPRSS2) plays an important role in breaking down the spike protein into S1 and S2 subunits, thereby S2 facilitates the process of binding the virus to the host cell membrane [27,28]. The Renin-Angiotensin system (RAS) is regulated by ACE2 (Fig. 1). Accordingly, a diminution in ACE2 activity after coronavirus infection could lead to RAS dysfunction, which impresses the blood pressure and electrolyte/fluid level, and boost inflammation and permeability of vascular in the respiratory system [29,30]. When SARS-CoV2 contaminates cells expressing the membrane surface ACE2 receptors and TMPRSS2, replication and diffusion of the virus induce the cell to encounter pyroptosis and release some factors related to cell injury, including nucleic acids, ATP, and ASC oligomers. These molecular factors can be identified by adjacent endothelial cells, epithelial cells, and lung alveolar macrophages, leading to the production of chemokines and pro-inflammatory mediators like CXCL10, IL-6, macrophage inflammatory protein 1α (MIP1α), MIP1β, and monocyte chemoattractant protein 1 (MCP1). These protein factors bring macrophages, monocytes, and T lymphocytes to the local of infection, increasing subsequent inflammation with high levels of interferon (IFN)-γ released by T cells and beginning a new pro-inflammatory response. In an incomplete immune reaction, this may assist in the reposition of immune system cells in the lungs, resulting in a mass production of pro-inflammatory cytokines that finally damages the lung tissue. In addition, the resulting cytokine storm spreads to other

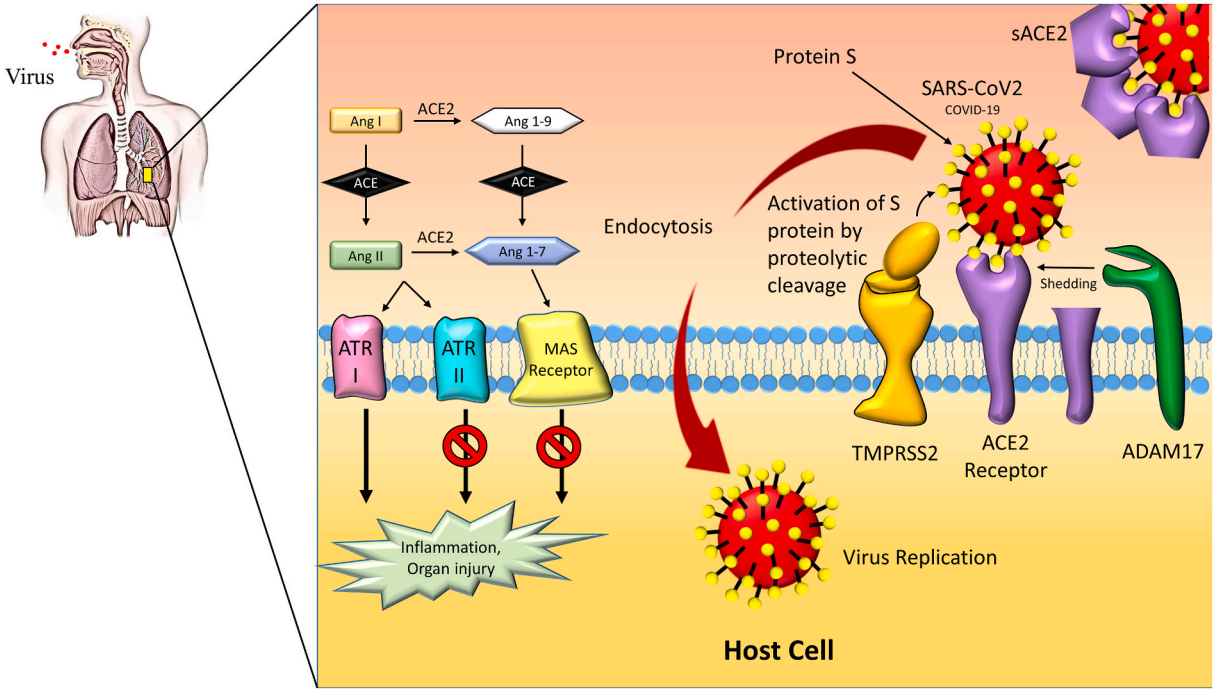

Fig. 1. After activation of the S subunit protein on the COVID-19 surface by transmembrane protease serine 2 (TMPRSS2), the virus binds to the Angiotensin-converting enzyme 2 (ACE2) receptor and infects the host cell through endocytosis. ACE2 is also separated from the cell membrane by A disintegrin and metalloproteinase 17 (ADAM17), and change to the soluble form of ACE2 that prevents the virus binding to ACE2 receptor in the host cell membrane and would have useful effects of defense against lung damage but not infection with COVID-19. Another important function of Angiotensin-converting enzyme (ACE) is controlling organ injury and inflammation via the renin-angiotensin system. Briefly, another important function of ACE is controlling organ injury and inflammation via the renin-angiotensin system. Angiotensin-converting enzyme (ACE) transform angiotensin type I (Ang I) to angiotensin type II (Ang II), and Ang II intracellular signaling pathway causes inflammation as well as organ injury through the type 1 of Ang II receptor (ATR I) and has reverse effects through the type 2 of Ang II receptor (ATR II). Angiotensin-converting enzyme 2 (ACE2) converts Ang I to Ang- [1–9] and Ang II to Ang- [1–7]. Ang- [1–7] blocks the effects of inflammation via the Mas receptor.

tissues and can damage several organs [31].

3.1. T cell response

T cell responses against SARS-CoV-2 are discovered in the blood about 7 days after the beginning of disease symptoms. CD8+ T cells are substantial for outright clearing of virus-infected cells, while CD4+ T cells are important to improve the function of both B cells and CD8+ T cells by secreting a wide range of mediators [23]. Despite reports regarding lymphopenia and decreased peripheral blood T cells in patients, these explorations propose that T cells are summoned from the blood into the contaminated area to restrict the disease. In patients with severe COVID-19, augmented T cell infirmity and lessened functional diversity cause intense form of the disease [32–34]. COVID-19 specific CD4+ T cells express tumor necrosis factor (TNF)-α, IL-2, and IFN-γ, which indicates that patients with COVID-19 present a helper T (Th) 1 response and mostly utilize cellular immunity to eliminate the infection [35].

On the other hand, SARS-CoV-2 can infect human T cells through CD147, which is expressed on the T cell surface. Additionally, CD147 is expressed in lots of cells and tissues and has a major role in cell apoptosis, proliferation, migration, differentiation, and metastasis, particularly under the hypoxic situation, of tumor cells [36].

Once SARS-CoV-2 enters into the target cells, viral peptides are presented by class I major histocompatibility complex (MHC I) proteins to the CD8+ T cells. After that, CD8+ T cells are activated and triggered for cell division and move toward clonal expansion and expand virus-specific memory and effector T cells. CD8+ T cells lyse cells infected by virus. Not only complete virus but also viral particles are recognized by specific antigen-presenting cells (like dendritic cells (DCs) and macrophages) and present viral peptides to CD4+ T cells via MHC Class-II molecules. B cells can identify causative disease agent and get activated in two ways, one by direct pathway and the other by interaction with CD4+ T cells [37].

Despite the limited immune response, preliminary studies show patients who recovered from COVID-19 developed specific memory T cells against virus, which were traceable within 24 months after recovery [38].

3.2. B cell response

About 7 days after the onset of first symptoms in patients with COVID-19, the response of B cells with the assistance from follicular helper T cells can be assessed. In patients with COVID-19 infection, the B cell response is usually first against the N protein, then antibody responses to the S protein are found within 4–8 days after the onset of symptoms [39,40]. Protective antibodies are produced in the second week of illness, often in response to protein S, but most people have neutralizing antibodies in the third week. Additionally, the principal target of the neutralizing antibodies produced in COVID-19 is a part of the S1 protein subunit. This region is called “receptor-binding-domain (RBD)” and is made up of 193 amino acids (amino acids 318–510). RBD is able to bind to the ACE2 expressed on the host cell and initiate the infection process [41–43].

The binding of the virus-antibody complexes to the Fc receptors on immune cells like alveolar macrophages could impel the production of pro-inflammatory proteins, including MCP1 and IL-8, which enhance the immune stimulatory conditions. These complexes agitate the complement system and result in another undesirable inflammation. Hence, it is substantial to consider designing therapeutic antibodies without pro-inflammatory effects and keep their neutralizing capacity against the virus. For example, changes in the Fc region of antibodies or its

glycosylation can modify its binding affinity to the Fc receptor [44–46].

A recent survey suggests that specific antibodies against the SARS-CoV-2 particles may only be preserved for 2 months. This causes a concern that effective immunity to the virus may not persist for a long term. Likewise, rapid reduction in the titer of antibodies have been illustrated in mild cases. However, with a half-life of nearly 21 days for IgG, it is expectable for titer reduction in COVID-19 patients. Laboratory studies on the level of IgM and IgG antibodies in subjects with COVID-19 indicate that these antibodies are also found in the asymptomatic individuals, but it is noteworthy that the antibody titer is much lower in such patients [47–49].

3.3. The role of other Immune system cells in COVID-19

Natural killer (NK) cells are part of the innate immune system, which have capability to target virus-infected cells [50]. NK cells have the potential to lysis abnormal target cells through cytotoxic mechanisms and ignore self-cells expressing MHC I. Investigations reported that cytotoxicity function of NK cells can controlled through a factor called inhibitory natural killer receptor [51]. Immune cell profile laboratory tests indicated that NK cell counts will reduce during COVID-19 infection because of infiltration into the sites that have been affected by COVID-19, like the lung [52–54]. NK group 2A (NKG2A) receptor as an inhibitory signaling transmitter, has some functional effects on T cells and NK cells, such as cytotoxicity reducing and cytokine secretion suppressing. Studies have shown in individuals who infected with SARS-CoV-2 the expression of NKG2A is dramatically high, while the expression level of markers like TNF-α, IL-2, IFN-γ, and CD107a is remarkably lower, as activator factors [54]. Besides, it is proved that the hyper activation of localized NK cells in the lung can be more damaging than beneficial and cause lung injury [55,56].

The main mission of neutrophils is the deletion of pathogens via the phagocytosis process. They also can release Neutrophil Extracellular Traps (NETs) for virus inactivation and cytokine to stop virus replication [57–59]. NETs contain chromatin fibers affiliated with some enzymes, including myeloperoxidase, cathepsin G, and neutrophil elastase [60]. NETs function is like to a double edge of sword; primary role of this traps has recorded in anti-inflammatory response and in opposite, they can develop tissue damage too [61,62]. The data analysis of a study reported that neutrophil degranulation and activation are highly activated processes in SARS disease [63]. Neutrophil penetration and localization in lung capillaries with migration to alveolar space was illustrated in lung autopsies sampled from patients who passed away from COVID-19, demonstrating inflammation in the lower overall part of the respiratory system [64,65]. On other hand, not only immature neutrophils but also inefficient mature neutrophils have been reported in SARS-CoV-2 patients [66]. Broncho alveolar fluid testing from COVID-19 patients recorded great levels of CXCL-8 and CXCL-2, chemokines that simplify the neutrophils recruitment to the infection zone [67,68], and extended activation of these phagocytic cells may lead to harmful effects in the respiratory system and cause ARDS [69]. In addition, neutrophils secrete toxic factors that might contribute to ARDS too [70]. Some of ROSs like H2O2 and superoxide radicals can produced follow a respiratory burst by neutrophil cells. Finally, this mechanism develop oxidative stress that associates with blood clots and cytokine storm in COVID-19 patients [71].

Monocytes are a kind of leukocytes that are deriving from myeloid progenitors and circulate in the blood. They have a plasticity character and the capacity to differentiate into other cells such as dendritic cells and macrophages [72]. Monocytes are categorized into two principal subgroups with various characterization. For instance, [1]: CD14++CD16− monocytes that named as classical cells; [2]: CD16+ monocytes that classified to CD14++CD16+ cells and CD14 + CD16++ (non-classical) [73]. After the COVID-19 infection, some of the monocyte's functional roles are impaired, including chemotaxis and cytokine secretion. Nowadays, a pattern of remodeled cytokine profiles, as well as chemokine, has been proved in monocytes of COVID-19 patients. This altered in cell's products contributes to a chain of incompetent responses, which subsequently boost the damaging of SARS-CoV-2 and cause a raise in mortality [74,75]. All in all, reduced monocyte cell count has been recorded in infected patients by the surveys and explained that the phenotype of monocytes in intense cases frequently consists of CD14+ monocytes, and CD16+ inflammatory monocytes which applies inflammatory activity through IL-6 secreting in COVID-19 [76].

4. Mesenchymal stem cells and COVID-19

Today, incredible advances have been achieved in the treatment of diseases through cell therapy, particularly stem cells, which have provided a bright horizon for incurable patients [77]. Mesenchymal stem cells (MSCs) have several unique properties including many resources for cell purification, self-renewal, high proliferation, non-invasive procedure to obtain, immunosuppression, and multidirectional differentiation. These cells can transform into adipocytes, chondrocytes, and osteocytes in the induction medium [78]. There are many advantages to apply MSC therapy as a new method in analogy with other available treatments. They are more accessible and can be separated and purified from several tissues, such as the umbilical cord blood, menstrual blood, bone marrow, adipose tissues, buccal fat pad, dental pulp, fetal liver, etc. The effectiveness and safety of MSCs have been evidently approved in several clinical trial studies (Table 1) [79]. Additionally, MSCs have extensive clinical usage outlooks, including as a remedy for ARDS. Some of the bioactivities of MSCs are immunomodulating effects, enhanced alveolar fluid, clearance, alignment of respiratory endothelial permeability, and repair [80].

It has been shown that various soluble agents secreted by MSCs are involved in regulating the immune system. Exosomes, as an extracellular vesicle of MSCs, have indicated well-appointed abilities to protect against various organ damages, regenerate, and repair, which may play a major function in the treatment of ARDS. Furthermore, because of the low homing of MSCs following injection (trapped in the capillaries of the lungs, low expression of CXCR4), MSCs colonization to the injured area is also the goal of running clinical studies [81–83]. However, a small number of cells may reach the target tissue, but still have positive effects because they are able to remain stable in the damaged tissue and play a role in improving tissue repair by regulating the immune system. So, today there are bright prospects for the treatment of SARS-CoV-2 by MSCs, and extensive research is being done around the world in this area [84].

4.1. Therapeutic effects of MSCs

The International Society of Cell Therapy has set three criteria for MSCs that it must meet in order to be utilizable in the clinics. First, MSCs must have the property of adhering to plastic when maintained under suitable culture protocols. Second, they must express some specific markers, such as CD73, CD90, and CD105, and not express CD11b, CD14, CD45, CD79a, CD34, CD19, and human leukocyte antigen (HLA)-DR molecules. Third, MSCs must be able to differentiate into adipocytes, chondroblasts, and osteoblasts in vitro [85]. MSCs ought to express modest ratio of MHC class I molecules. However, they should not express MHC class II and other stimulant molecules, including CD80, CD86, and CD40, leading to low immunogenicity of MSCs. Given these features, it can be assumed that these cells do not elicit an immune response in the recipient and have already been used in clinical trials [86,87].

Several lines of researches have spent a lot of time on the potential of MSCs to discharge paracrine factors like immune regulatory factors, cell migration factors, and angiogenic factors. These cytokines promote MSCs migration and their homing to damaged tissues for repair. Other ways have also been attended, and it has been demonstrated that MSCs interact with recipient tissues through straight interactions between cells. The useful effects of MSCs are basically associated with paracrine

Table 1
Summarized clinical trial (recruiting and completed) studies on the MSCs in the COVID-19 (https://www.clinicaltrials.gov).

	NCT Number	Title	Status	Source of MSC	Interventions	Phase	Population	Locations	Results or aims
1	NCT04444271	Mesenchymal Stem Cell Infusion for COVID-19 Infection	Recruiting	Bone marrow	•Drug: Mesenchymal stem cells •Other: Placebo	2	20	NIBMT, Rawalpindi, Punjab, Pakistan	Assessing the efficacy of MSCs as an add-on therapy to standard supportive treatment
2	NCT04416139	Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19	Recruiting	Umbilical cord	•Biological: Infusion IV of Mesenchymal Stem cells	2	10	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico	Describing the clinical changes secondary to IV administration of MSC allogenic, in patients with bilateral COVID-19 pneumonia complicated by severe ARDS, with the evaluation of the PaO2 / FiO2 ratio, heart and respiratory rates, and the fever curve.
3	NCT04313322	Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells	Recruiting	Wharton's Jelly	•Biological: WJ-MSCs	1	5	Stem Cells Arabia, Amman, Jordan	Investigating the potential use of Wharton's Jelly Mesenchymal stem cells for COVID-19
4	NCT04713878	Mesenchymal Stem Cells Therapy in Patients With COVID-19 Pneumonia	Completed	n/a	•Other: Mesenchymal stem cells	n/a	21	University of Health Sciences, Istanbul, Turkey	Recording the mortality status, procalcitonin and C-reactive protein values, leukocyte values, comorbid diseases, interleukin −2, interleukin −6, Tumor necrosis factor-alpha-beta, and CD4 as well as CD8
5	NCT04252118	Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19	Recruiting	n/a	•Biological: MSCs	1	20	Beijing 302 Military Hospital of China, Beijing, China	Investigating safety and efficiency of MSCs in treating pneumonia patients infected with SARS-CoV-2
6	NCT04611256	Mesenchymal Stem Cells in Patients Diagnosed With COVID-19	Recruiting	Adipose tissue	•Biological: MSC •Drug: Control	1	20	Hospital Regional Lic Adolfo Lopez Mateos, Mexico City, Ciudad De Mexico CDMX (Mexico City), Mexico	Implement adjuvant therapy with adipose tissue derived-mesenchymal stem cells (MSCs) for critical COVID-19 patients
7	NCT04339660	Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia	Recruiting	Umbilical cord	•Biological: UC-MSCs •Other: Placebo	1, 2	30	Puren Hospital Affiliated to Wuhan University of Science and Technology, Wuhan, Hubei, China	Explore therapeutic potential of MSCs for COVID-19 pneumonia patients
8	NCT04336254	Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients	Recruiting	Dental pulp	•Biological: allogeneic human dental pulp stem cells (BSH BTC & Utooth BTC) •Other: Intravenous saline injection (Placebo)	1,2	20	Renmin Hospital of Wuhan University (East Campus), Wuhan, Hubei, China	Evaluate the safety and efficacy of allogeneic human dental pulp mesenchymal stem cells in the treatment of severe pneumonia caused by COVID-19
9	NCT04753476	Treatment of Severe COVID-19 Patients Using Secretome of Hypoxia-	Recruiting	n/a	•Biological: Injection of Secretome-MSCs •Drug: Standard treatment of Covid-19	2	48	•Sultan Imanuddin Hospital, Kalimantan, Central Borneo, Indonesia	Evaluating the improvement in clinical, laboratory, and radiological manifestations in

(*continued on next page*)

Table 1 (*continued*)

	NCT Number	Title	Status	Source of MSC	Interventions	Phase	Population	Locations	Results or aims
		Mesenchymal Stem Cells in Indonesia						•Charlie Hospital, Kendal, Central Java, Indonesia •RS PKU Muhammadiyah Yogyakarta, Yogyakarta, Central Java, Indonesia	treated patients compared with the control group
10	NCT04565665	Cord Blood-Derived Mesenchymal Stem Cells for the Treatment of COVID-19 Related Acute Respiratory Distress Syndrome	Recruiting	Cord blood	•Other: Best Practice •Biological: Mesenchymal Stem Cell	1	70	•M D Anderson Cancer Center, Houston, Texas, United States	Assess the safety of administering cord blood derived mesenchymal stem cell (CB-MSC) infusions for treatment of COVID-19 acute respiratory distress syndrome (ARDS)
11	NCT04288102	Treatment With Human Umbilical Cord-derived Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)	Completed	Umbilical Cord	•Biological: UC-MSCs •Biological: Saline containing 1% Human serum albumin (solution without UC-MSCs)	2	100	•General Hospital of Central Theater Command, Wuhan, Hubei, China •Maternal and Child Hospital of Hubei Province, Wuhan, Hubei, China •Wuhan Huoshenshan Hospital, Wuhan, Hubei, China	Result: UC-MSCs significantly reduced the proportions of solid component lesion volume compared with the placebo
12	NCT04573270	Mesenchymal Stem Cells for the Treatment of COVID-19	Completed	n/a	•Biological: PrimePro •Other: Placebo	1	40	•Southern California Hospital at Culver City / Southern California Hospital at Hollywood, Culver City, California, United States	Investigating the safety and efficacy of stem cell therapy for the treatment of patients admitted to hospital suffering complications from COVID-19 and the treatment of healthy subjects (healthcare providers) for prophylactic effect following those patients.
13	NCT04366063	Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome	Recruiting	n/a	•Biological: Cell therapy protocol 1 •Biological: Cell therapy protocol 2	2,3	60	•Royan Institute, Tehran, Iran, Islamic Republic of Iran	Assess the safety and efficacy of Mesenchymal Stem Cells (MSC) for the treatment of ARDS in COVID-19 patients
14	NCT04629105	Regenerative Medicine for COVID-19 and Flu-Elicited ARDS Using Longeveron Mesenchymal Stem Cells (LMSCs) (RECOVER)	Recruiting	Bone marrow	•Biological: Longeveron Mesenchymal Stem Cells (LMSCs) •Other: Placebo	1	70	•Miami VA Healthcare System, Miami, Florida, United States •University of Maryland Medical Center, Baltimore, Maryland, United States •Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, United States	Testing the safety of LMSCs in Adults suffering from mild to severe acute respiratory distress syndrome (ARDS) due to COVID-19 resultant from 2019-nCoV coronavirus infection, or resultant from influenza virus infection
15	NCT04366271	Clinical Trial of Allogeneic Mesenchymal Cells From Umbilical Cord	Recruiting	Umbilical Cord	•Biological: Mesenchymal cells •Drug: Standard of care	2	106	•Hospital Universitario de Getafe, Getafe, Madrid, Spain	Propose a therapy with undifferentiated allogeneic

(*continued on next page*)

Table 1 (*continued*)

	NCT Number	Title	Status	Source of MSC	Interventions	Phase	Population	Locations	Results or aims
		Tissue in Patients With COVID-19						•Hospital Universitario de Cruces, Barakaldo, Spain •Hospital Universitario de La Princesa, Madrid, Spain	mesenchymal cells derived from umbilical cord tissue
16	NCT04390152	Safety and Efficacy of Intravenous Wharton's Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID 19	Recruiting	Wharton's Jelly	•Drug: Wharton's jelly derived Mesenchymal stem cells. •Drug: Hydroxychloroquine, lopinavir/ritonavir or azithromycin and placebo (standard therapy)	1,2	40	•BioXcellerator, Medellin, Antioquia-CO, Colombia •Clinical Somer, Rionegro, Antioquia, Colombia	Investigating the effects of Wharton's Jelly Derived Mesenchymal Stem Cells in the COVID-19
17	NCT04457609	Administration of Allogenic UC-MSCs as Adjuvant Therapy for Critically-Ill COVID-19 Patients	Recruiting	Umbilical Cord	•Drug: Oseltamivir •Drug: Azithromycin •Biological: Umbilical Cord Mesenchymal Stem Cells	1	40	•Cipto Mangunkusumo General Hospital, Jakarta Pusat, DKI Jakarta, Indonesia •Persahabatan General Hospital, Jakarta, DKI Jakarta, Indonesia	Mesenchymal Stem Cell therapy
18	NCT04397796	Study of the Safety of Therapeutic Tx With Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation	Recruiting	Bone marrow	•Biological: BM-Allo. MSC •Biological: Placebo	1	45	•St. Francis Medical Center, Lynwood, California, United States	Evaluating the preliminary safety and efficacy of BM-Allo.MSC vs placebo in treating subjects with severe disease requiring ventilator support during COVID 19 infection
19	NCT04390139	Efficacy and Safety Evaluation of Mesenchymal Stem Cells for the Treatment of Patients With Respiratory Distress Due to COVID-19	Recruiting	Wharton-Jelly mesenchymal stromal cells	•Drug: XCEL-UMC-BETA •Other: Placebo	1,2	30	•Hospital de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain •Mútua de Terrassa, Terrassa, Barcelona, Spain	Assessing the efficacy and safety of 2 infusions of Wharton-Jelly mesenchymal stromal cells (day 1 and day 3, endovenously at 1E6cells/Kg per dose) in patients with moderate acute respiratory distress syndrome (ARDS) secondary to SARS-CoV-2 infection. Follow-up will be established on days 3, 5, 7, 14, 21, and 28. Long term follow-up will be performed at 3, 6 and 12 months
20	NCT04461925	Treatment of Coronavirus COVID-19 Pneumonia (Pathogen SARS-CoV-2) With Cryopreserved Allogeneic P_MMSCs and UC- MMSCs	Recruiting	Placenta	•Procedure: Placenta-Derived MMSCs; Cryopreserved Placenta-Derived Multipotent Mesenchymal Stromal Cells •Drug: Antibiotics •Drug: Hormones •Drug: Anticoagulant Therapy •Device: Oxygen therapy	1,2	30	•Institute of Cell Therapy, Kyiv, Ukraine	Assessment of the clinical effects of infusions of cryopreserved allogeneic multipotent mesenchymal stem cells of the placenta and umbilical cord for COVID-19 patients with acute respiratory distress syndrome
21	NCT04392778	Clinical Use of Stem Cells for the Treatment of Covid-19	Recruiting	n/a	•Biological: MSC Treatment •Biological: Saline Control	1,2	30	•Istinye University, Istanbul, Turkey •SBÜ Dr. Sadi	The aim of this study is using the regenerative and repair abilities of

(*continued on next page*)

Table 1 (*continued*)

	NCT Number	Title	Status	Source of MSC	Interventions	Phase	Population	Locations	Results or aims
								Konuk E#itim ve Ara#t#rma Hastanesi, Istanbul, Turkey	stem cells to fight against the harmful effects of the novel coronavirus Covid-19
22	NCT04355728	Use of UC-MSCs for COVID-19 Patients	Completed	Umbilical cord	•Biological: Umbilical Cord Mesenchymal Stem Cells + Heparin along with best supportive care. •Other: Vehicle + Heparin along with best supportive care	1,2	24	•Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, Florida, United States	The purpose of this research study is to learn about the safety and efficacy of human umbilical cord derived Mesenchymal Stem Cells (UC-MSC) for treatment of COVID-19 Patients
23	NCT04269525	Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019- novel Coronavirus(nCOV) Pneumonia	Recruiting	Umbilical Cord	•Biological: UC-MSCs	2	16	•Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China	This study is conducted to find out effects of UC-MSC in COVID-19
24	NCT04535856	Therapeutic Study to Evaluate the Safety and Efficacy of DW-MSC in COVID-19 Patients	Completed	n/a	•Drug: allogeneic mesenchymal stem cell •Other: Placebo	1	9	•Site 550: University of Hassanudin/ Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia	This is a phase 1 clinical trial to verify the safety and efficacy of DW-MSC in COVID-19 patients
25	NCT03042143	Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST) (COVID-19)	Recruiting	Umbilical cord	•Biological: Human umbilical cord derived CD362 enriched MSCs •Biological: Placebo (Plasma- Lyte 148)	1,2	75	•Belfast Health and Social Care Trust, Royal Hospitals, Belfast, Northern Ireland, United Kingdom	The primary objective of the study is to assess the safety of a single intravenous infusion of Mesenchymal Stromal Cells (MSCs) in patients with Acute Respiratory Distress Syndrome (ARDS) due to COVID-19. Secondary objectives are to determine the effects of MSCs on important clinical outcomes
26	NCT04537351	The MEseNchymal coviD-19 Trial: a Pilot Study to Investigate Early Efficacy of MSCs in Adults With COVID-19	Recruiting	n/a	•Biological: CYP-001	1,2	24	•Nepean Hospital, Kingswood, New South Wales, Australia •Westmead Hospital, Westmead, New South Wales, Australia •Footscray Hospital, Footscray, Victoria, Australia •Sunshine Hospital, Saint Albans, Victoria, Australia	This is a pilot, multi-centre, open-label randomized controlled study to assess the early efficacy of intravenous (IV) administration of CYP-001 in adults admitted to an intensive care unit (ICU) with COVID-19
27	NCT04466098	Multiple Dosing of Mesenchymal Stromal Cells in Patients With ARDS (COVID-19)	Recruiting	n/a	•Biological: Mesenchymal stromal cells •Other: Placebo	2	30	•University of Minnesota, Minneapolis, Minnesota, United States •University of Pittsburgh, Pittsburgh,	This is a multi-center, randomized, placebo controlled, interventional phase 2A trial to evaluate the safety profile and potential efficacy of

(*continued on next page*)

Table 1 (*continued*)

NCT Number	Title	Status	Source of MSC	Interventions	Phase	Population	Locations	Results or aims
							Pennsylvania, United States	multi-dosing of mesenchymal stromal cells (MSC) for patients with SARS-CoV-2 associated Acute Respiratory Distress Syndrome (ARDS)

mechanisms [88].

One of the reasons for exacerbated disease activity in patients with COVID-19 has been reported to underlie in the production of pro-inflammatory cytokines. MSCs confer beneficial therapeutic properties in treating the COVID-19 patients due to their anti-inflammatory effect. MSCs can diminish the inflammatory settings through regressing the cytokine storm derived by COVID-19, promoting the secretion of IL-10 (which can decrease the inflow and congestion of neutrophils inside the lung), and alleviate the generation of TNF-α [89,90].

Keratinocyte growth factor (KGF) produced by MSCs leads to the recovery of injury, contributes to the renovation of lung alveolar epithelial cells, and also trigger the proliferation of epithelial cells by augmenting surface-active factors, including Interleukin-1 receptor antagonist (IL-1RA), matrix-metalloprotein 9 (MMP)-9, Granulocyte-macrophage colony-stimulating factor (GM-CSF), etc. Conforming to the latest clinical results, endothelial cells of the lung can play an important function over the course of SARS-CoV-2 infection as a remedial target. MSCs play a role in stabilizing endothelial barrier function by increasing the permeability of respiratory capillaries through producing HGF and Vascular endothelial growth factor (VGEF). By stopping apoptosis of pulmonary vascular endothelial cells, raising the level of Vascular endothelial (VE)-cadherin, and detracting pro-inflammatory factors, MSCs defend the lung endothelial barrier and control inflammation. Due to the fact that the virus infects the lungs, MSCs have the potential to significantly settle in lung tissue after infusion and can be used as a promising treatment option in COVID-19 patients (Fig. 2) [91–94].

4.2. Exosome of MSCs

MSCs are able to release small vesicles (with a dimension of 30 nm – 150 nm) called exosomes that contain nucleic acids like mRNA and microRNA (miRNA) and cellular proteins [95,96]. Since the finding of exosome vesicles as a paracrine vesicle of the MSCs, researches have inquired about their potential in finding out the mechanistic and regenerative facets in treating diseases. The utilization of MSC-derived exosomes as a cell-free therapy has acceptable advantages over cell therapy, such as low immunogenicity, high stability, ability to cross the blood-brain barrier, and easy storage approaches [97]. These exosomes have a bilipid membrane structure that possess biocompatibility

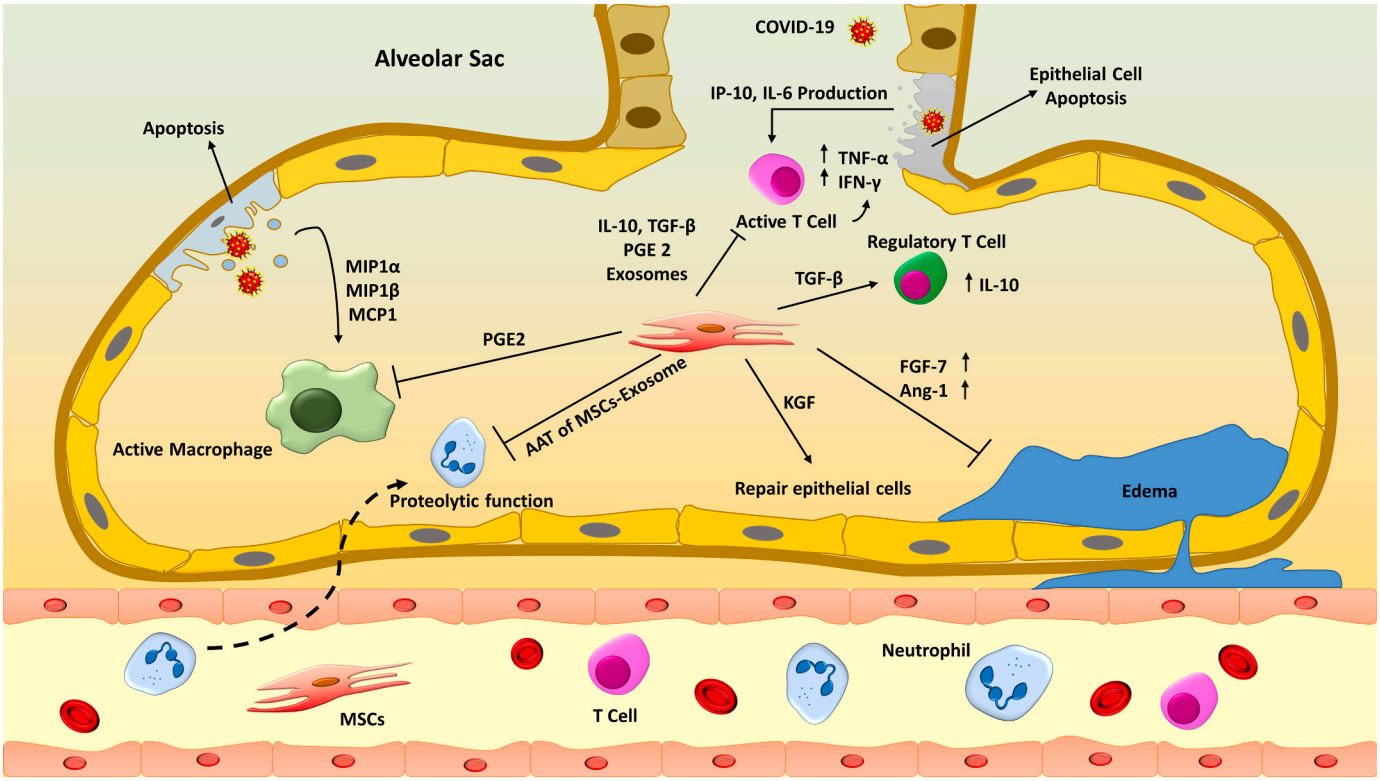

Fig. 2. Epithelial cells infected with the SARS-CoV-2 in the alveolar sac produce pro-inflammatory cytokines (IL-6, CXCL10) that lead to T cell activation. Activated T cells produce inflammatory cytokines (TNF-α, IFN-γ) leading to an intensive inflammation that can be stopped by IL-10, TGF, PGE2, and MSC-derived exosomes. In addition, regulatory T cells under the influence of TGF-β released from MSCs, produce IL-10 that is involved in reducing the inflammatory response. Alpha-1-antitrypsin (AAT) plays an important role in suppressing the proteolytic activity of neutrophils called to the site of infection by active macrophages.

potential that confer these extra-cellular vesicles as an ideal option among the drug delivery systems. Thus, exosomes have obtained enough scores in evaluating their functional role as pharmacological and therapeutic intermediation in dealing with the SARS-CoV-2 pandemic (Fig. 3) [98,99].

As mentioned earlier, epithelial cell damage is one of the most serious risk factors for the COVID-19, therefore it is important to generate and protect them against undesirable damage, potentially through exosomes [100]. In a survey by Bari et al., it was shown that exosomes of mesenchymal cells express Alpha-1-anti trypsin (AAT) on the surface. This structure inhibited neutrophil-derived proteolytic enzymes and also exhibited anti-inflammatory and immune-regulating effects that favor the protection of lung epithelial cells [101].

During infection by SARS-CoV-2, cytokine storm is observed due to the ruinous immune system response leading to major lung injuries. This is mainly started by pro-inflammatory macrophages that are settled inside the lungs. A divergence from pro-inflammatory cells secreting cytokines like TNF-α, IL-1β, IL-8, and IL-6 to an anti-inflammatory macrophage with immune prohibitory cytokines (like Transforming growth factor (TGF)-β and IL-10) by MSCs-derived exosomes may improve the undesirable consequences of the disease. New evidences indicate that macrophages type 2 (M2) are able to release factors that are necessary in the reduction of inflammation and tissue repairing that lead to wound healing. Several investigations have shown that exosomes can alter macrophages phenotype from the M1(pro-inflammatory) to the M2 (anti-inflammatory) [102]. Some preclinical studies have discussed the effect of exosomes on the lung macrophages, hence researchers have considered a variety of protocols to recover the lungs pathogenicity associated with COVID-19. These pre-clinical studies have reported that the attendance of miR-145 and proteins in exosomes derived from MSCs increases the lung tissue maintenance and regeneration. Furthermore, exosome vesicles may also adjust the function of lung DCs via over-expression of immune suppressing cytokines, such as TGF-β and IL10, thus prohibiting the lungs from the harmful macrophage cells and immune response related to DCs [103–105].

Pulmonary edema is inevitable following impairment of the endothelial and epithelial barrier of the lungs and increased permeability of the alveolus during infection. This unexpected physiological mechanism disrupts the air exchange action of the lung. One animal study revealed that MSCs-derived exosomes detract extravascular lung fluid by 43% with a decline in pulmonary edema and permeability of lung [106]. This potential of exosomes was partly mediated by CD44-dependent pathway of exosomes for localization inside the injured host cells [107].

Therefore, it appears that with the assistance of high potential that exosomes have in accelerating the healing of damaged lung tissue, promising insights have been raised in the treatment of COVID-19 patients and can be prescribed as a nano-medicine.

4.3. *Exosomes as a drug delivery vehicle*

Today, among the most suitable drug carriers for drug delivery are liposomes or vesicles with phospholipid membranes [108]. Exosomes have lots of positive characteristics that are impressive in their role as drug delivery vehicles. They help implement a defensive barrier against premature transformation and omission. Liposomes can easily constitute hydrophobic and/or hydrophilic drugs in their hydrophobic membranes or within an aqueous core, respectively. They can also break the plasma membrane to release their loaded medication. Liposomal membranes have potential to insert modified antibody segments or ligands on their surface, facilitating the interaction with specific target cells, conferring specific drug delivery. They may also be developed with an inert polymeric structure like polyethylene glycol to decrease liposome

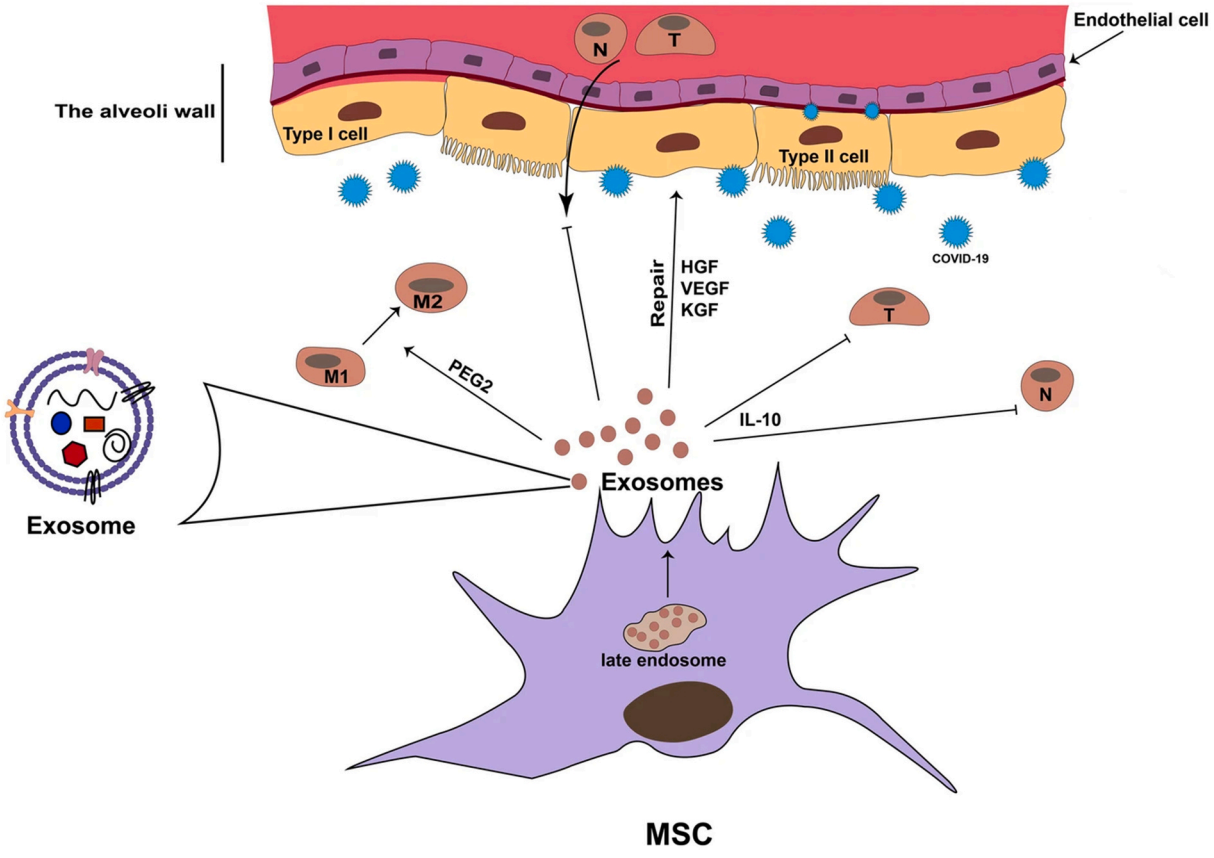

Fig. 3. The role of MSC-derived exosomes in the treatment of COVID-19. N: Neutrophil; M1: Macrophage type I; M2: Macrophage type II; T: T lymphocyte. Figure is reused from Springer Nature publisher [118].

identification by opsonins and elimination of the liposomes. Amid the several secreted membrane carriers, exosomes are the most appropriate for expansion as a drug delivery carrier [109]. Firstly, the attendance of nucleic acids and protein in MSCs-derived exosomes annotates that such biological molecules could be placed into exosomes. Secondly, exosomes are sustained in the body ideally, as demonstrated by their immense dispensation in biological fluids [110]. Thirdly, exosome vesicles are able to pass through the plasma membrane to transfer their loaded pharmaceutical cargo into the target cells. For instance, DCs-derived exosomes can transmit peptide-packed MHC class II and I complexes to another DC to regulate the immune response [111]. Fourthly, exosomes have an inherent potency to target tissues. Exosomes have special homing target sites depending on the sources from which they are derived [112]. Finally, exosomes are flexible to membrane rectification that augment targeting of a specific cell [113].

5. Hypothesis of exosome drug delivery systems designing in COVID-19

Clinical achievements of the medications targeting the COVID-19 requires the recognition of a proper transfer system that improves medicine absorption and facilitate an easy intracellular transfer, while preserve drug concentration between the lungs and the systemic circulation of drug. The targeted transfer of the loaded drug via the carriers guarantees the best activity on the objective target and least toxicity, while adjusted delivery systems maintain an effectual medicine concentration over the target area and reducing the constant density of the loaded drug, thereby reducing the unwanted effects. Routinely, several methods have been used for drug delivery such as nano-theranostics, drug-antibody conjugates, and vesicular drug delivery. Previous investigations have reported the potential of exosomes as well as other methods of drug delivery systems features, hence we can get a purposeful and efficient new drug delivery system with modifying of exosome properties in the COVID-19 patients.

5.1. Nano-theranostics

Nasal delivery of drug-carrying theranostic nanoparticles is presented as a successful treatment strategy to control the COVID-19. These types of drug carriers can be classified into three different categories, including inorganic, organic as well as virus-like structures or self-assembly tiny proteins. The vehicle system impressively dominates the drug delivery difficulties related to the mucosal track and retain a highly effective dose of the medicine at the local of infection, while expressing little side effects to the healthy tissues and cells [114].

5.2. Drug-antibody conjugates

The medication particles are bonded to the antibodies by a chemical reaction and release their cargo at the target site. Preclinical data have documented that SARS-CoV-2 antibody STI-1499, that entirely inhibited the viral contamination. The antibody reportedly stopped the viral dispersion by blocking the interaction of ACE2 with the S1 subunit of the virus, a necessary incident for the entry of the COVID-19 into the host cells [115].

5.3. Vesicular drug delivery

The vesicular drug delivery method gives an interesting innovatory approach as theranostics in COVID-19 cases. Mainly, the surface charge existent on the vesicular carrier plays an important function in deciding the pharmacokinetics related to a cargo drug molecule. The attendance of positive charge on the surface of the vesicular system as a carrier causes its adhesion to the mucosal membrane with negative charge via an electrostatic binding and inhibits their enzymatic degradation and mucociliary clearance. Importantly, studies on the vesicular drug delivery systems indicated improved residence time of medicine, while extending their release at the object site. These kinds of drug carrier systems establish the co-delivery of therapeutics with proper adjuvants and sustain a high density of the cargo molecules at the intended site [116]. Recently, researchers have been able to completely encode the S-protein subunit by means of mRNA1273 encapsulated in lipid nanoparticles. T cells that identify the COVID-19 antigen rapidly escalate an immunological response in the cells expressing this specific viral protein. This can be a confident and prosperous strategy as it does not utilize viral particles, and thus prepares mRNAs that may be expressed by non-immune and immune cells. In addition, encapsulation of lipid nanoparticles causes decreased viral mRNA degradation and more efficiency during administration [117].

6. Conclusion

The recent COVID-19 pandemic in the world is one of the most tragic events that has killed thousands of patients. Due to the long duration of the window period, most of the patients become infected without the early signs of the disease. Therefore, these people as carriers have a direct role in the increasing prevalence of the disease, making it difficult to control the disease. COVID-19 establishes prolonged chemokine and cytokine responses in severe cases of the disease, known as the cytokine storm. Cytokine storm motives ARDS or several-organ dysfunction, which causes death. Well-time inhibition of the cytokine storm in its early phase through cytokine antagonists and immune-modulators, also the diminution of inflammatory cell infiltration into the lung, is the most vital goal in order to treat and alleviate the mortality rate related to COVID-19. The great benefits of using MSCs along with exosomes have changed the focus on these drug carriers. The exosomes released by MSCs are a new strategy for treating the COVID-19 due to their immune regulatory role and regenerative property. According to clinical studies on this novel therapeutic intervention, exosomes can be regarded as a cell-free therapy and drug delivery system. Nonetheless, further clinical studies are required to disclose the potency of MSCs and related exosomes in the treatment of COVID-19 patients.

Authors' contributions

Conceptualization, writing original draft and funding acquisition: **Homayoon Siahmansouri**. Supervision, validation, review, and editing: **Majid Ahmadi**. Literature searching: **Meruyert Dauletova**, Manuscript revision performing, response to reviewers, and final editing: **Hafsan Hafsan, Negah Mahhengam,** and **Angelina Olegovna Zekiy.**

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Data availability

Not applicable.

Ethical approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Consent to participate

Not applicable.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be considered as a potential conflict of interest.

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