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Mini Review

Immunomodulatory effect of mesenchymal stem cells and mesenchymal stem-cell-derived exosomes for COVID-19 treatment

Authors:

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Running Title: Mesenchymal stem cell-derived exosomes as COVID-19 therapy.

Keywords : COVID-19; Immunomodulation; Mesenchymal stem cells (MSCs); Exosome; Therapy; Ongoing Clinical trials.

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Abstract

The world has witnessed unimaginable damage from the coronavirus disease-19 (COVID-19) pandemic. Because the pandemic is growing rapidly, it is important to consider diverse treatment options to effectively treat people worldwide. Sincethe immune system is at the hub of the infection, it is essential to regulate the dynamic balance in order to prevent the overexaggerated immune responses that subsequently result in multiorgan damage. The useof stem cells as treatment options has gained tremendous momentum in the past decade. The revolutionary measures in science have brought to the world mesenchymal stem cells (MSCs) and MSC-derived exosomes (MSC-Exo) as therapeutic opportunities for various diseases. The MSCs and MSC-Exos have immunomodulatory functions; theycan be used as therapy to strike a balance in the immune cells of patients with COVID-19. In this review, we discuss the basics of the cytokine storm in COVID-19, MSCs, and MSC-derived exosomes and the potential and stem-cell-based ongoing clinical trials for COVID-19.

Introduction

The world has been facing a dreadful situation due to the spread of the Severe Acute Respiratory Syndrome–Coronavirus-2 (SARS-CoV-2)(1). However, neither confirmed effective antiviral medications nor vaccines are available to deal with this emergency (2). Many reports have suggested that it isthe cytokine storm in COVID-19 that leads to acute respiratory distress syndrome (ARDS) (3). The cytokine storm in COVID-19 refers to the fact

thata variety of cytokines are rapidly produced after viral infections (4). In addition, such acytokine storminduceshypoxia, and direct viral infection can cause cellular damage. Multiorgan damage and injury have been concomitant with COVID-19, and can be observed more in patients with a more severe form of the disease(5).

Stem cells are specialized cells that can renew themselves by means of cell division and can differentiate into multilineage cells. Mesenchymal stem cell (MSCs) have immunomodulatory features and secrete cytokines and immune receptors that regulate the microenvironment in the host tissue (6). In addition, it has been observed that the crucial role of MSCs in therapy has been mediated by exosomes released by the MSCs. These exosomes have exhibited immunomodulatory, antiviral, anti-fibrotic, and tissue-repair- related functions *in vivo;* similar effects have been observed *in vitro* (6).

COVID-19 and the immune system

The dynamic equilibrium maintained by innate and adaptive immunity is essential for impeding the progression of COVID-19(7). In patients infected with SARS-CoV-2, the plasma levels of IL-1β, IL-1RA, IL-7, IL-8, IL-10, IFN-ɣ, monocyte chemoattractant peptide (MCP)-1, macrophage inflammatory protein (MIP)-1A, MIP-1B, G-CSF, and TNF-α are significantly higher than in controls. The levels of these factors are also increased in patients who were admitted to ICUs (8). Similarly, reductions in the levels of T cells and NK cells have been observed in COVID-19 patients (9). The loss of such cells can impair the immune system (10). The levels of the helper T cells, cytotoxic suppressive T cells, and regulatory T cells are much lower in patients with COVID-19 than in their healthy and less severe counterparts. The decrease in the regulatory T cells may hamper theirability to inhibit the chronic inflammation (11). Interestingly, a remarkable increase is observed in the naïve T cells,whereasthe memory T cells are reduced in infected patients(10). The reduced expression of memory cells may be a plausible explanation for the increased rates of reinfection by SARS-CoV-2.

The cytokine storm

SARS-CoV-2 binds to the Angiotensin-converting enzyme 2 (ACE2) receptor and enters the host cell(1). During infection, the innate and adaptive immune systems work together to inactivate the virus. Since leukocytes and neutrophils are present in higher concentrations in COVID-19 individuals, these immune cells may result in the cytokine storm (10).After viral entry, the virus induces pyroptosis and cell death. The dead cells recruit macrophages to the site of injurythat phagocytose them. The phagocytes then express damage-associated molecular patterns (DAMPs), which bind to the toll-like receptors (TLR) and induce nuclear factor kappa B (NF-κβ) signalling by means of the MyD88 pathway. NF-κβ enters the nucleus and catalyzes the transcription of pro-IL-1β and procaspase-1. When additional signals are detected, the pro-IL-1β and procaspase 1 are cleaved into IL-1β and caspase 1 (12). The activated NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) recruits the apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and pro-caspase-1 to form the NLRP3 inflammasome (13). In addition, the phagocytosis releases ATP, which binds to the P2X purinoceptor 7 (P2RX7) and activates the inflammasome (14). The increased calcium levels caused by the viral proteins results in lysosomal damage, thereby releasing cathepsins that activate the inflammasome (15). Further, the binding of SARS-CoV-2 to the ACE2 reduces the available ACE2 receptors on the cell surface. This increases the levels of Angiotensin II (AngII) in the extracellular space, because ACE2 converts AngI and AngII into Ang 1-9 and Ang1-7, respectively. AngII increases the levels of TNF-α and IL-6 in the cell that upregulates NF-κβ, activating the inflammasome (12). The continuous activation of the inflammasome results in a cytokine storm, which recruits more immune cells, necrosis, and cell death. This inflammasome pathway further causes tissue injury in various organs (Figure 1).

MSCs and immunomodulation

MSCs are predominantly isolated from the bone marrow, adipose tissue, dental pulp, umbilical cord, Wharton's jelly, placenta, synovial fluid, endometrium, and peripheral blood. These cells exhibit different cell-surface markers and can be used for a variety of treatment options (Table 1). MSCs can undergo*in vitro* amplification and self-renewal, and have low immunogenicity and immune-modulatory functions; the latter have attracted attention in clinical trials (16). MSCs have been widely used in various cellular therapies, such as pre-clinical studies, as well as in some clinical trials, because of their high safety and efficacy (17, 18). MSCs can exert immune-modulatory effects in the host cells of both the innate and the adaptive immune system. The direct or indirect interactions of MSCs with the immune cells makes the MSCs activate the immunomodulatory responses (19). The immunomodulatory functions of MSCs depend on the environment of the host cells; based on the inflammatory status, the MSCs decide the type of immunoregulatory effect (20). MSCs represent pro-inflammatory immune reactions and anti-inflammatory reactions (21). MSCs regulate the immunesystem via the transforming growth factor β1 (TGFβ1), which can trigger the proliferation of Tregs, induce IL-6, which prevents the proliferation of neutrophils, and stimulate the prostaglandin E2 (PGE2),which inhibits the antigen presentation by dendritic cells and proliferations of T-effector cells (22,23). MSCs mediate these kinds of effects by direct contact, where it releases the regulatory cytokines, such as IFN-γ, indoleamine 2,3-dioxygenase,TGFβ , IL -10, and PGE2 (24). Moreover, MSCs can hinder the proliferation and/or functions of the CD4+ Th1 and TH17 cells, CD8+ T cells, and the natural killer(NK)cells, mainly by secreting soluble factors, such as TGFβ1 and hepatocyte growth factor (HGF) (16).

Mesenchymal Stem Cells (MSCs) and MSC secretome

It has currently become apparent that MSCs induce therapeutic characteristics by a paracrine pathway by releasing bioactive substances known as secretomes (25). MSC-secretomes are made of soluble proteins, including cytokines, chemokines, growth factors,

and extracellular vesicles (EVs),which include microvesicles and exosomes (26). Stem cells release these secretomes by common secretory mechanisms. When the culture medium or secretome are injected into the patients, the neighboring cells assimilate the molecules by paracrine signalling (27). The exosomes themselves contain numerous bioactive molecules, which include microRNAs (miRNA), transfer RNAs (tRNA), long noncoding RNAs (lncRNA), growth factors, proteins, and lipids. The lipid content of the exosomes provide an added advantage by aiding in the infusion of the exosomes with the plasma membrane of the neighboring cells (28). The molecules involved in regulation of cell growth, proliferation, survival, and immune responses are released by exosomes, are elaborately illustrated in Figure 2. Upon internalization of the molecules in the secretome, the neighboring cells modulate various downstream pathways,including immunomodulation, suppression of apoptosis, prevention of fibrosis, and remodelling of the injured tissues (25).

Immunomodulatory potential of MSC-Exos

Exosomes are nanoparticles with a diameter of 40-150 nm. To generate and isolate the exosomes, MSCs can be conditioned to increase the release of exosomes by treatment with cytokines or by serum starvation or hypoxia (29). The exosomes are then purified and can be subsequently introduced into the body. MSC-Exos can inhibit CD4+ and CD8+ T cells and NK cells (30). They inhibited T cells expressing IL-17and induced IL-10-expressing regulatory cells that are involved with suppression of inflammation. MSC-Exos also aid in suppressing the differentiation of CD4+ and CD8+ T cells by releasing molecules like TGFβ and prevent inflammation *in vivo* (31). Similarly, treatment with MSC-Exos reduced the proliferation and activation of NK cells (32). MSC-Exos could shift macrophages from the M1 to the M2 phenotype, further suppressing pro-inflammatory states (33). Moreover, sepsis is an important lethal factor in COVID-19 patients, and treatments with MSC-Exos have increased the rate of survival in mice with sepsis (34). Concomitantly, MSC-Exos also suppressed release of the proinflammatory factors TNF-α, IFN-γ, IL-6, IL-17, and IL-1β (35)

and promoted release of anti-inflammatory factors, such asIL-4, IL-10 and TGF-β (36). Additionally, MSC-Exos also reduced the number of chemokines in the serum when injected (37). These immunomodulatory effects of MSC-Exos have also been attributed to their anti-inflammatory cargo, such as IDO, HLA-G, PD-L1 and galectin-1(38) (39). These mechanisms are illustrated in Figure 3.

MSC-Exos therapy for COVID-19

In COVID-19, multiorgan damage has been seen in manyinfected individuals. MSC-Exos might alleviate lung injury in asthmatic models and ARDS (40) (41). MSC-Exos may also be useful in the treatment of cardiovascular (42) and renal problems (43). Hence, they can be used to treat organ damage associated with COVID-19. Similarly, MSC-EVs have also exhibited inhibitory activity on the hemagglutination of avian, swine, and human influenza viruses (44). Likewise, MSC-Exos lowered the death rate in H7N9 patients without any toxic effects during follow-up examinations (45). In addition, these exosomes consist of adhesion molecules that accurately guide them to the injured site. The usage of the exosomes may be preferred to the MSCs, since they can easily cross the blood-brain barrier, are inexpensive, and cannot undergo independent self-renewal, hence preventing adverse consequences, such as tumor formation. In this pandemic situation, MSC-Exos may be a good treatment options to alleviate the effect of SARS-CoV-2 infection.

Current clinical trials of stem cell-based therapy in COVID-19

Of late, stem-cell-based studies in the treatment of COVID-19 have been gaining momentum. The efficiency and safety of usage of exosomes that had been obtained from BM-MSCs was recently tested on 24 SARS-CoV-2 patients(46). These patients exhibited moderate to severe ARDS. When the exosomes were introduced into the patients, there were no side effects, and patients improved in clinical status and oxygenation(46). Inasimilar study, patients treated with MSCs showed a remarkable improvement in pulmonary function, higher levels of peripheral lymphocytes, and a reduction in the cells that trigger the cytokine storm.

Interestingly, the MSCs did not exhibit ACE2 or TMPRSS2 expression, showing that they may not be infected with COVID-19 (47). Several clinical trials are in the pipeline for usage of stem cells for the treatment of COVID-19 (Table 2). Wharton's jelly-derived MSCs (WJ-MSCs), which have been used in various studies based on stem-cell therapyand trials, are in progress for their usage for COVID-19 treatment (48). Moreover, adipose tissue-derived AD-MSCs have been used in a few studies in variousdoses and protocols for COVID-19 therapy (49).Likewise, a novel trial includes inhalation of MSC-Exos for alleviation of symptoms(50).In addition, MSCs from dental pulp (51) and olfactory mucosa (52)were administered in variousdoses. MSCs in the clinical trials are predominantly administered intravenously; i.v. injection and, in some studies, MSCs have been given as adjuvant therapy in addition to drugs like oseltamivir, hormones, hydroxychloroquine, and azithromycin (53) (54). These trials reveal promising new routes for the battle against COVID-19 (55-94).

Future directions

Stem cells have been studied extensively for their ability to regenerate and for the treatment of various diseases. Recently, we devised an improved protocol for the isolation of urine-derived stem cells and their further differentiation into immune cells (95). Moreover, our research group promoted the hematopoietic differentiation of hiPSCs using a novel small molecule (96). At the advent of COVID-19, it has become mandatory to discover therapeutic strategies that are easily reproducible and cost effective. Drugs currently available for the treatment of COVID-19 include ones that target viral replication. These drugs include camo-stat mesylate, which is involved in the inhibition of viral fusion to the cell membrane, and favipiravir and remdesivir, which are anti-viral drugs. However, because the cytokine storm is found predominantly in COVID-19 patients, it is essential to consider drugs that inhibit viral replication while treating the cytokine storm. Hence, MSC-Exos may be appropriate therapeutic targets for COVID-19 (97). MSCs can be more advantageous than other anti-inflammatory agents, because they can provide immunomodulatory effects based on the host

cells. In addition to these effects, MSCs can prevent fibrosis of tissues, enable reversal of lung dysfunction, and aid in the regeneration of damaged tissue, which can be significantly beneficial for COVID-19-associated organ damage (98) (99). Becausethe healing properties of the MSCs can be primarily attributed to the secretomes or exosomes, using them may be more effectivethan using MSCs themselves. Exosomes can be mass-produced, administered systematically with minimaltoxicity, and be able to reach the cell targets more efficiently.In addition to their inherent immunomodulatory potential, the MSC-Exos can also be used as a drug-delivery system (100). MSC-Exos can be modified *invivo* to release exosomes that have a higher immunomodulatory potential(101) and can be cultured using various cytokines to exhibit an anti-inflammatory state (102).Although MSC-Exos appear to be promising therapeutic agents for COVID-19, more experimental research is necessary for them to be used clinically. Moreover, it is essential to optimize the protocols for storage and isolation of MSC-Exos for the treatment of COVID-19. It is also imperative to do experiments to understand the underlying mechanisms of COVID-19 in order to optimize MSC-Exo therapy for treatment (97). Further, it is also essential to find theoptimum dosage, route of administration, and treatment schedule for MSC-Exos. Hence, sinceMSCs are more widely studied in these aspects than are MSC-Exos, they are predominantly preferred in clinical trials for COVID-19 (103).

Concluding remarks

COVID-19 has invoked frenzy in individuals worldwide. The unceasing increase ofinfection and death has halted the livesof the citizens of countries everywhere. Hence, it is important to discover novel therapeutic platforms and productive measures without further delay (104). The therapies produced must be easily reproducible and available in large quantities so that enoughbioactive molecules will be available for all individuals who have succumbed to COVID-19. MSCs and MSC-Exos can be used for their immunomodulatory effects in individuals with COVID-19.

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CONFLICTS OF INTEREST

The authors have no conflicting interest.

FIGURE LEGENDS

Figure 1. Role of cytokine storm in COVID-19

When SARS-CoV-2 binds the cell, the ACE2 receptors become occupied. This increases AngII which results in lung fibrosis, inflammation, and damage. The infected cell also undergoes cell death as a result of the viral infection. Macrophages engulf the dead cells and release DAMPSs, which bind the TLR and activated NF-κβ by means of MyD88. Activated NF-κβ binding activates the inflammasome. Binding of the virus to the receptor also upregulatesIL-6 and TNF-alpha, further activating NF-κβ. Increase in ATP binds theP2X7 receptor, which in turn increases Ca2+, which causes lysosomal damage and further activation of the inflammasome. Continuous activation of the inflammasome produces the cytokine storm, resulting in multiorgan damage.

Figure 2. Molecules released by MSC-Exos. MSC-Exos affect their targets by means of various molecules that they secrete. The MSC-Exos secrete molecules that maintain the homeostasis in the neighboring cells while also secreting glycolytic enzymes. Other molecules involved in cell growth, proliferation, and modulation of the immune response and

signalling pathways are secreted by the MSC-Exos. Some membrane-bound molecules that aid in cell signalling and miRNAs with various functions are also released by MSC-Exos.

Figure 3.MSC-Exos therapy for COVID-19. Isolated MSCs are conditioned in specialized media that induce release of exosome. The MSCs identify the external signal and start to pack regulatory factors in secretory vesicles that are released into the culture medium. The exosomes are identified and isolated using specific markers, and are then administered intravenously the i.v. injection. The exosomes inhibit IL-1, IL-6, NK cells, CD4+, and CD 8+. This results in suppression of the cytokine storm. Exosomes also activate IL-10, TGF-beta, M2 macrophages, and T and B regulatory cells to further suppress the immune system. This reduces the proinflammatory cytokines, alleviating symptoms and aiding in recovery of patients

Table 1. Commonly used sources of MSCs.

Table 2. Ongoing stem-cell-based clinical trials forCOVID-19.

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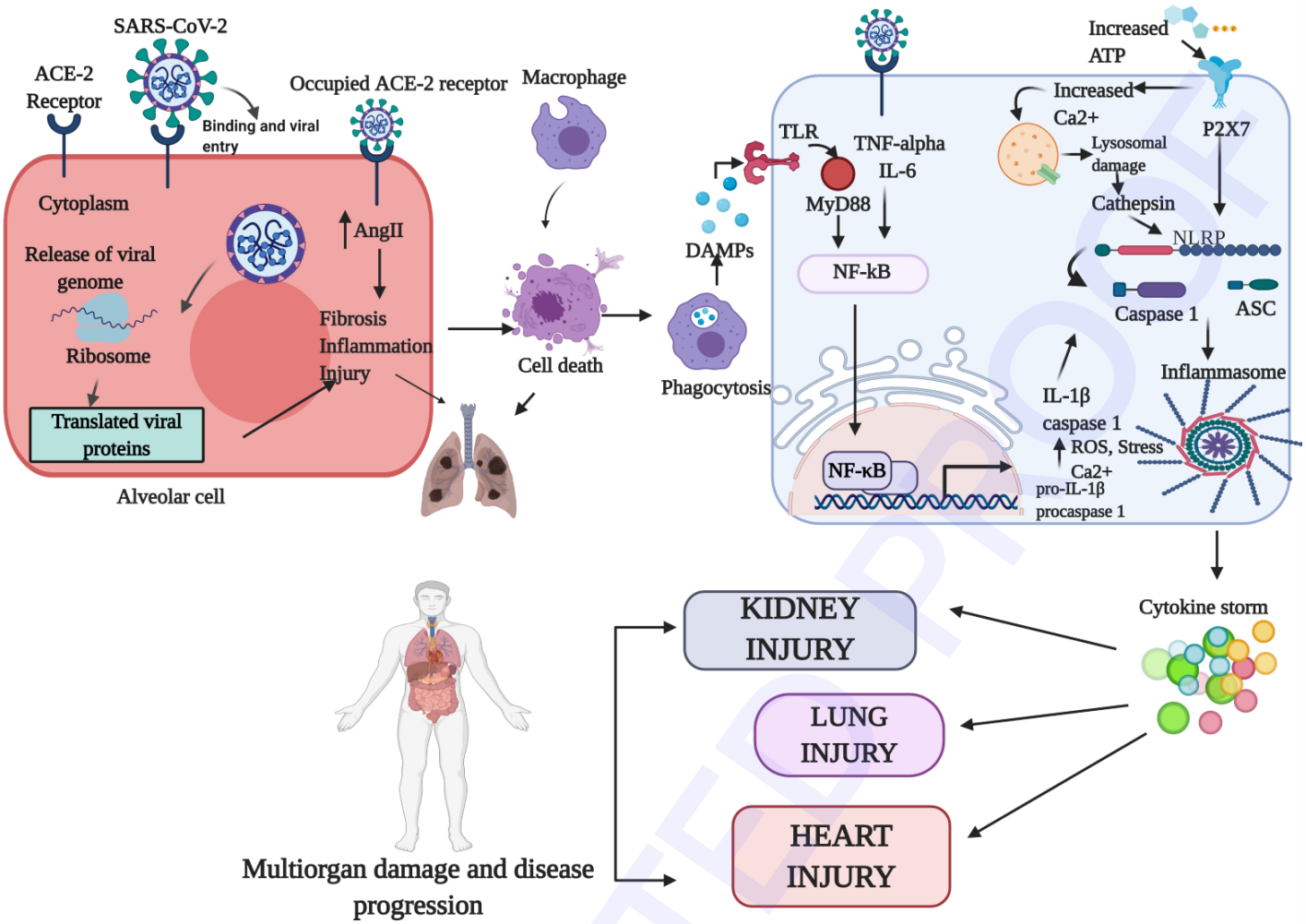

Fig. 1.

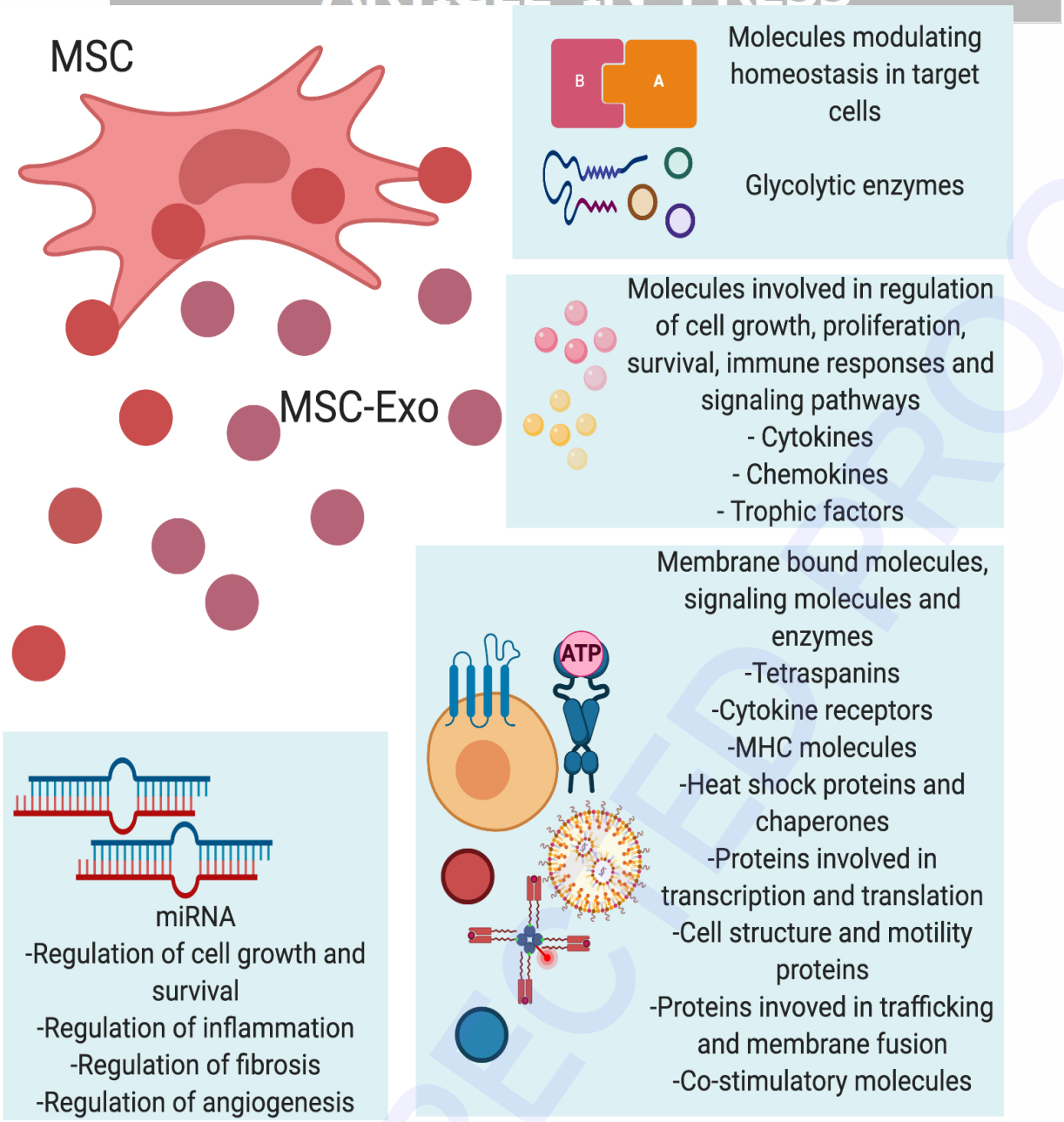

Fig. 2.

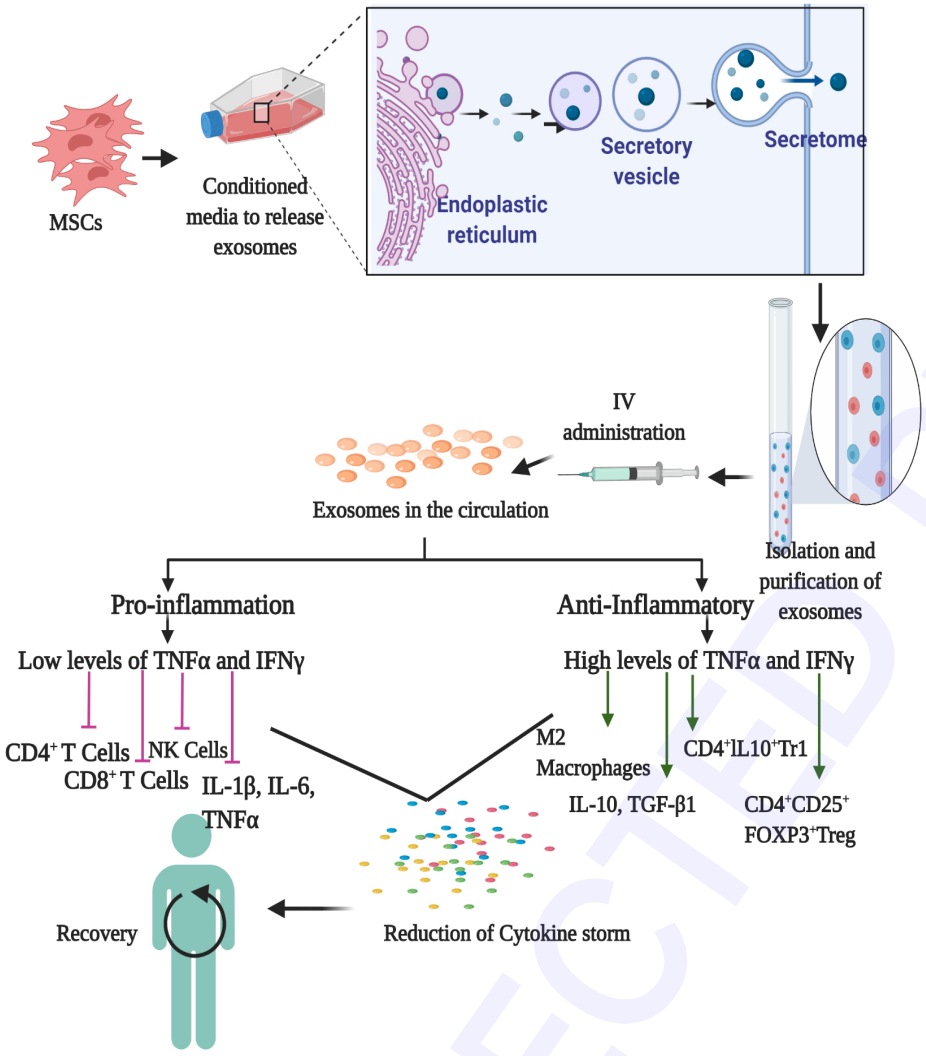

Fig. 3.

Table 1: Commonly used Sources of MSCs

S. No	Source	Extraction route	Purity level	Proliferation rate	Doubling time	MSCs Marker
1.	Bone Marrow	Bone Marrow Aspiration	High	Lowest	40 Hrs	Stro-1, CD271, SSEA-4, CD146
2.	Adipose Tissue	Liposuction, lipectomy	Medium	Higher	5 days	CD271, CD146
3.	Dental pulp	Tooth extraction or root canal	Low	High	30-40 Hrs	Stro-1, SSEA-4, CD146
4.	Umbilical Cord	After birth from umbilical cord	High	Medium	30 Hrs	CD146
5.	Wharton's jelly	After birth from umbilical cord	High	High	30 Hrs	CD73, CD90, CD105
6.	Placenta	Obtained after delivery	High	High	36 Hrs	SSEA-4, CD146
7.	Synovial Fluid	Synovium or synovial fluid	High	High	10 days	Stro-1, SSEA-4, CD146
8.	Endometrium	Endometrium biopsies or menstrual blood or	High	High	18-36 Hrs	Stro-1, CD146
9.	Peripheral Blood	Density Gradient Centrifugation	Low	Low	95 Hrs	CD133

Table 2: Ongoing stem cell based clinical trials in COVID-19.

Study title	Intervention	Study size	Description	Status	Country	Reference
Treatment of COVID-19 patients using Wharton's Jelly- Mesenchymal Stem Cells	WJ-MSCs	5	Dose: 3 IV doses of 1X10e6/kg. Time: 3 days apart	Phase 1	Jordan	55
Safety and Efficacy study of Allogenic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients	Allogenic Human Dental Pulp MSCs Placebo: Intravenous Saline	20	Dose: IV of 3.0x10e7 human dental pulp stem cell solution (30ml) on day 1, day 4 and day 7 IV of 3ml of 0.9% saline at the same interval	Phase 2	China	56
NestCell Mesenchymal Stem Cells to Treat Patients with Severe COVID-19 Pneumonia	NestCell	66	Dose: 2x10^7 cells (20 million cells) Time: days 1, 3 and 5 in addition to standard care. On day 7, cells will only be administered if necessary.	Phase 1	Brazil	57
A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Allogeneic Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19	HB-adMSCs	100	3 groups of patients, will receive five IVs at 200, 100 and 50 million cells/dose. Infusions will occur at week 0, 2, 6, 10 and 14. Placebo is saline.	Phase 2	USA	58
Clinical Trial to Assess the Safety and Efficacy of Intravenous Administration of Allogeneic Adult Mesenchymal Stem Cells of Expanded Adipose Tissue in Patients With Severe Pneumonia Due to COVID-19	Allogenic expanded adMSCs	26	Two doses of 80 million adipose-tissue derived mesenchymal stem cells	Phase 2	Spain	59
A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences	HB-adMSCs	56	Dose: five IV infusions	Phase 2	USA	60

Autologous Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19			Time: follow-up inflammatory data will be obtained at 6, 14, 26 weeks; and PHQ-9 Questionnaires at weeks 2,6,10, 14, 18, 22, 26			
Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem cells	Dental pulp MSCs	24	Dose: 1.0x106 cells /kg. The injection of dental mesenchymal stem cells will be increased on day 1, 3 and 7	Early Phase 1	China	51
Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19	MSCs	20			China	61
Treatment With Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)	MSCs Saline containing 1% Human serum albumin （solution of MSC）	90	3 times of MSCs(3.0*10E7 MSCs intravenously at Day 0, Day 3, Day 6)	Phase 1	China	62
Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID-19)	BM-MSCs	20	Participants will receive conventional treatment plus BM-MSCs (1*10E6 /kg body weight intravenously at Day 1)	Phase 2	China	63
Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Severe COVID-19	UC-MSCs	48	4 times of UC-MSCs (0.5*10E6 UC-MSCs/kg body weight intravenously at Day 1, Day 3, Day 5, Day 7)	Not yet recruiting	China	64
Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment	Drug: Oseltamivir and	60	Umbilical cord mesenchymal stem cells were given at 106/Kg body weight / time, once every 4 days for a total of 4	Early Phase 1	China	53

of Pneumonia of Coronavirus Disease 2019	hormones MSCs		times. Peripheral intravenous infusion was given within 3 days of first admission			
Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia	UC-MSCs	30	1*10E6 UC-MSCs /kg suspended in 100mL saline	Phase 2	China	65
Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome	Cell therapy	60	Protocol 1(n=20). Two doses of MSCs 100×10e6 (±10%) at Day 0 and Day 2 plus Conventional treatment. Protocol 2: Two doses of MSCs 100×10e6 (±10%)at Day 0 and Day 2, intravenously plus two doses of EVs at Day 4 and Day 6 plus conventional treatment.	Phase 3	Iran	66
Role of Immune and Inflammatory Response in Recipients of Allogeneic Haematopoietic Stem Cell Transplantation (SCT) Affected by Severe COVID19	No intervention	40	Comparison of biomarkers	Active, not recruiting	United Kingdom	67
Use of UC-MSCs for COVID-19 Patients	UC- MSCs	24	UC-MSC will be administered at 100x10^6 cells/infusion administered intravenously in addition to the standard of care treatment	Phase 2	USA	68
Stem Cell Educator Therapy Treat the Viral Inflammation in COVID-19	Stem Cell Educator -Treated Mononuclear Cells Apheresis	20	SCE therapy circulates a patient's blood through a blood cell separator, briefly cocultures the patient's immune cells with adherent CB-SC in vitro, and returns the autologous immune cells to the patient's circulation.	Phase 2	USA	69

Efficacy and Safety Study of Allogeneic HB-adMSCs for the Treatment of COVID-19	Drug: HB-and MSC Drug: Placebo Drug: HC Drug: AZ	110	Dose: 4 IV of HB-adMSCs at 100 million cells/dose+ hydroxychloroquine and azithromycin. HB-adMSC infusions will occur at day 0, 3, 7, and 10. Placebo: similar intervals without the HB-adMSCs	Phase 2	USA	54
Therapy for Pneumonia Patients Infected by 2019 Novel Coronavirus	Biological: UC-MSCs	N.A	0.5*10E6 UC-MSCs /kg body weight suspended in 100mL saline containing 1% human albumin intravenously at Day1, Day3, Day5, Day7	Withdrawn	China	70
Battle Against COVID-19 Using Mesenchymal Stromal Cells	Allogeneic and expanded adipose tissue-derived MSCs	100	Two serial doses of 1.5 million adipose-tissue derived mesenchymal stem cells/ kg	Phase 2	Madrid	71
Safety and Efficacy of CAStem for Severe COVID-19 Associated With/Without ARDS	CAStem	9	A dose-escalation with 3 cohorts with 3 patients/cohort who receive doses of 3, 5 or 10 million cells/kg.	Phase 2	China	72
ASC Therapy for Patients With Severe Respiratory COVID-19	Stem Cell Product	40	100 million allogeneic adipose-derived mesenchymal stromal cells diluted in 100 ml saline	Phase 2	Denmark	73
Mesenchymal Stem Cells (MSCs) in Inflammation-Resolution Programs of Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS)	MSC	40	Infusion of allogeneic bone marrow-derived human mesenchymal stem (stromal) cells	Phase 2	Germany	74

Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus (nCOV) Pneumonia	UC-MSCs	10	UC-MSCs infusion intravenously on day 1, day 3, day 5, and day 7.	Phase 2	China	75
A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia	MSCs-derived exosomes	30	5 times aerosol inhalation of MSCs-derived exosomes (2.0*10E8 nano vesicles/3 ml at Day 1, Day 2, Day 3, Day 4, Day 5).	Phase 1	China	50
MultiStem Administration for COVID-19 Induced ARDS (MACoVIA)	MultiStem	400	IV infusion of MultiStem	Phase 3	USA	76
Cell Therapy Using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS	UC Wharton's jelly-derived human Placebo: NaCl 0.9%	60	Dose: 1 million/kg through an intravenous route	Phase 2	France	48
Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID_MSV)	Mesenchymal Stromal Cells	24	IV injection of 1 million MSV cells/Kg diluted in 100 ml saline	Phase 2	Spain	77
Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease)	Mesenchymal Stromal Cells	30	Dose:1 x 10^8 MSCs through IV	Early Phase 1	USA	78
Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST) (COVID-19)	Remestemcel-L	300	Administered twice during the first week, with the second infusion at 4 days following the first injection (± 1 day)	Phase 3	USA	79
Treatment of Covid-19 Associated Pneumonia With Allogenic Pooled	Allogenic pooled	40	IV injection	Phase 2	Minsk	52

Olfactory Mucosa-derived Mesenchymal Stem Cells	olfactory mucosa-derived MSCs					
Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19	Autologous adMSCs	200	3 doses of 200 million cells through IV every 3 days	Phase 2	USA	49
Mesenchymal Stem Cell Infusion for COVID-19 Infection	MSCs	20	Dose: 2 x 106 cells/kg, administered on day 1,7 in addition to supportive care	Phase 2	Pakistan	80
Safety and Efficacy of Mesenchymal Stem Cells in the Management of Severe COVID-19 Pneumonia (CELMA)	UC-MSCs	30	Dose: 1*10^6 cells/Kg	Phase 2	USA	81
Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19 (COVID-19)	MSC	10	Dose: 1 million /Kg	Phase 2	Mexico	82
NestaCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia (HOPE)	NestaCell®	90	Dose : 2x10^7 cells on days 1,3,5 and 7	Phase 2	Brazil	83
Treatment With Human Umbilical Cord-derived Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)	UC-MSCs	100	Dose: 3 of 4.0*10E7 cells at Day 0, Day 3, Day 6.	Phase 2	China	84
Efficacy of Intravenous Infusions of Stem Cells in the Treatment of COVID-19 Patients	MSCs	20	IV injection of Cultured stem cells at days 1, 3 and 5	Phase 2	Turkey	85
Clinical Use of Stem Cells for the Treatment of Covid-19	MSCs	30	Dose: 3 million cells/kg on days 0, 3 and 6	Phase 2	Turkey	86
Safety and Efficacy of Intravenous Wharton's Jelly Derived	WJ-MSCs	40	2 doses	Phase 2	Colombia	87

Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID 19						
MSCs in COVID-19 ARDS	Remestemcel -L	300	Twice in the first week with a gap of 4 days between the injections	Phase 3	USA	88
Efficacy and Safety Evaluation of Mesenchymal Stem Cells for the Treatment of Patients With Respiratory Distress Due to COVID-19 (COVIDMES)	WJ-MSCs	30	Administration along with standard care	Phase 2	Spain	89
Cellular Immuno-Therapy for COVID-19 Acute Respiratory Distress Syndrome - Vanguard (CIRCA-19)	MSCs	9	IV administration	Phase 1	Canada	90
ACT-20 in Patients With Severe COVID-19 Pneumonia	Allogenic UC-MSCs	70	1 million cells / kg body weight in 100 ml in conditioned media	Phase 2		91
Study of the Safety of Therapeutic Tx With Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation	Allogenic BM-MSC	45	IV administration	Phase 1	USA	92
Double-Blind, Multicenter, Study to Evaluate the Efficacy of PLX PAD for the Treatment of COVID-19	MSCs	140	15 IM injections (1 mL each). Twice with an interval of 1 week	Phase 2	USA	93
A Study of Cell Therapy in COVID-19 Subjects With Acute Kidney Injury Who Are Receiving Renal Replacement Therapy	MSCs and a plasmapheresis device	24	Administered through integration into a Continuous Renal Replacement Therapy circuit	Phase 2		94

WJ: Wharton's Jelly; MSC: Mesenchymal stem cells; adMSCs : adipose derived MSCs; UC: Umbilical cord; IV: Intravenous; BM: Bone marrow; HC: hydroxychloroquine; AZ: azithromycin.