Review Article

Stem Cell INVESTIGATION

Virology of SARS-CoV-2 and management of nCOVID-19 utilizing immunomodulation properties of human mesenchymal stem cells—a literature review

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Objective: The objective of this review article is to outline the pathology, virology and mechanism of severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2) and to study the regenerative role of mesenchymal stem cells (MSCs) to tackle the lung damage caused by SARS-CoV-2.

Background: The MSCs possess trophic potentialities which enable them to find out the sites of injury or inflammation and because of their pleiotropic and pericytic nature, these cells are capable of differentiating into different cell types. The MSCs can be derived from a variety of tissue sources be it adult or embryonic origin. The one major characteristic of MSCs is that they are immunologically naïve in terms of expression of MHC Class II. This very low or no expression of MHC class II makes them useful in clinical settings where they can be used in allogenic transplant cases. This allogenic transplant possibilities of these MSCs makes them one of the most researched stem cells and investigated for cell-based therapies. Though these MSCs are in clinical settings for long the one even more important characteristic which makes them even more in demand is their immunomodulatory properties which have been used in various cases to mitigate the effect of overstimulation of the immune system. In recent times after the pandemic of the novel corona virus disease 2019 (nCOVID-19) generated by SARS-CoV-2, the effect of various MSCs isolated from various tissue sources are being utilized to curb the overstimulation of immune response, so that the immune system can be brought under some regulation to ultimately reduce the effect of inflammation.

Methods: In this review article, we have reviewed the existing literature, data and ongoing clinical trials by using keywords like novel coronavirus, COVID-19, SARS-CoV-2, MERS-CoV, acute respiratory distress syndrome, mesenchymal stem cells, immunomodulation properties of stem cells, regenerative properties of stem cells, cell therapy, clinical trials of stem cells, clinical trials of COVID-19 and stem cells till 20th August 2020 using database named PubMed, NCBI, Google Scholar, Scopus, Research Gate and Clinicaltrials.gov.

Conclusions: Thus, concluding the therapeutic potential of MSCs in managing and treating COVID-19.

Keywords: Corona virus disease 2019 (COVID-19); coronavirus; mesenchymal stem cell (MSC); immunomodulation; lung diseases

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Introduction

Stem cells are cells in nut cell can be defined as obligatory, asynchronous replicators. These cells are mesengenic cells, meaning they give rise to the tissue such as muscle, cartilage, bone, tendon, dermis, marrow stroma, connective tissues and fat (1,2). Human mesenchymal stem cells (hMSCs) are characterized by a set of markers (CD29, CD44, CD73, CD90, CD105) and lack the expression of CD14, CD34, CD45 and human leukocyte antigen (HLA) as proposed in 2006 by the International Society for Cellular Therapy (3). These cells reside in the pockets in almost all organs of an adult individual and protect the body from the general wear and tear process. Different pockets/niches in human body where MSCs reside are the heart (4), peripheral blood (5), cord blood (6), muscle (7), adipose tissue (8), lung (9), trabecular bone (10), intestine (11), kidney (12), liver (13), pancreas (14), synovium (15), skin (16), hair follicle (17,18), and even in the brain (19). These niches are specialized cell pockets that provide a necessary microenvironment for their survival and support.

Depending upon the origin of the tissue these stem cells are classified as adult stem cells (ASCs) or embryonic stem cells (ESCs). Differentiated adult stem cells which are induced to behave as pluripotent are called as induced pluripotent stem cells (iPSC) (20). Mesenchymal stem cells (MSCs) which are generally used in clinical settings are of adult origin. Though MSCs can be expanded from the embryonic stem cells the potential of undifferentiated embryonic stem cells to form teratoma (cancer of all the three germ layers) in nude mice generally limits their therapeutic potential (21). hMSCs in immune modulation have been reported in autoimmune diseases. Like inflammatory airway disorders (22), graft versus host disease (GVHD) (23) and in a disease model of autoimmune diseases such as systemic lupus erythematosus (SLE) (24) multiple sclerosis (25). In the recent outbreak if novel corona virus disease 2019 (nCOVID-19) pandemic hMSCs are being envisioned as a tool to modulate the immune response of the affected population and reports/reviews have started coming out wherein hMSCs are being used in the management of the nCOVID-19 (26-30).

A graphical abstract is available in the supplementary material (Figure S1). We present the following article in accordance with the narrative review reporting checklist (available at https://dx.doi.org/10.21037/sci-2020-040).

Virology of severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2)

The novel coronavirus disease 2019 (nCOVID-19) pandemic hits the present century so hard that the technology and economy freeze from its side effects (31). The coronavirus responsible for a nCOVID-19 pandemic is SARS-CoV-2 and is a new strain of coronavirus that hasn't been recognized in humans up until December 2019 (27). The Coronavirus has already caused the disease among humans however with different strains such as severe acute respiratory syndrome (SARS-CoV) and middle east respiratory syndrome (MERS-CoV) (27). Coronavirus enveloped with a positive-sense, single-stranded RNA genome (with nucleocapsid) ranged from 26-32 kb (32), which is the largest discovered RNA virus (27) in a genome with length structure and identity sequence is 79.6% identical to SARS-CoV (33). From the four (α, β, γ, δ) coronavirus genera, human coronavirus (HCoVs) is spotted in α coronavirus genera (NL63 and HCoV-229E) and β coronavirus genera (SARS-CoV, HCoV-HKU1, MERS-CoV and HCoV-OC43) (34). The β coronavirus genera indicate 88% identical with the sequence of two-bat derived severe acute respiratory syndrome (SARS)-like coronavirus, bat-SL-CoVZXC21 and bat-SL-CoVZC45 and nearly 50% identical to the sequence of MERS-CoV (34). Thus, the novel β-CoV was termed as "SARS-CoV-2" by the International Virus Classification Commission (35).

SARS-CoV-2 genome contains ten open reading frames (ORFs). The first open reading frame (ORF1a/b) are about 2/3rd of viral RNA, and are transferred into larger two polyproteins. In SARS-CoV and MERS-CoV, pp1a and pp1ab (two polyproteins) are processed into sixteen non-structured proteins (nsp1 – nsp16), which will further form the viral replicase transcriptase complex (35). Such non-structured proteins readjust Rough Endoplasmic Reticulum (RER) originating membranes towards double-membrane vesicles where transcription and viral replication occurs (36). The another open reading frames of SARS-CoV-2 on the

1/3rd of the genome encodes for four structural proteins named nucleocapsid (N), spike (S), envelope and membrane (M) protein as well as numerous accessory proteins with undefined role and don't have any role in viral replication (35).

Pathogenesis of SARS-CoV-2

SARS-CoV-2 affected patients come up with clinical manifestations including shortness of breath, dry cough, fever, fatigue, myalgia, evidence of pneumonia based on radiographic evidence, and decreased leukocyte counts (37), which are very much similar to SARS-CoV and MERS-CoV infections (38). Though the precious pathogenesis of SARS-CoV-2 is still poorly understood, but the overall mechanism of SARS-CoV and MERS-CoV open ups the information source on the pathogenesis of SARS-CoV-2 infection (27,31).

Interaction of virus protein with the human surface receptors

The S protein on coronavirus surface has been reported as a ticket to admission the virus into host cells (39) by recognizing the Angiotensin I converting enzyme 2 (ACE2) receptor by its spike protein (33,40,41). The enveloped spike glycol protein binds to its cellular receptor in the following manner as Angiotensin I converting enzyme 2 for SARS-CoV-2 (42) and SARS-CoV (43), CD209L (C-type lectin) called L-SIGN for SARS-CoV (44), DPP4 for MERS-CoV (45). Regrettably, the ACE2 receptor is distributed widely on the surface of human cells, specifically the alveolar type 2 of the lungs (46,47). The ACE2 receptor are also presents abundantly on heart, liver, kidney and digestive organs, altogether the smooth muscle cells and endothelial cells in organs express ACE2, thus the virus can enter speedily within the body through blood circulation (31). Thus, all the organs and tissue expressing Angiotensin I converting enzyme 2 could be involved in the battlefield of nCOVID-19 and explains why the patients suffering from respiratory distress syndrome also suffer from multiple organ dysfunction (MOD) including acute kidney shock, acute myocardial injury, shock and arrhythmia (28,37). Parallelly, a study done by Hoffmann *et al.* (48) demonstrated that cellular serine protease TMRRSS2 is needed to permit coronavirus entry into the host cells and it is plausible that human cells like capillary endothelium and alveolar type 2 (46) contains well distributed ACE2 receptor all over the surface and those alveolar type 2 cells largely express TMPRSS2 (48-50).

Back the coronavirus entry mechanism which is initiated by direct membrane fusion between the plasma membrane and the virus (50,51). Belouzard *et al.* (52) demonstrated a critical proteolytic cleavage incident occurred at S2' position of S protein in SARS-CoV medicated the membrane fusion and viral infectivity. In addition to membrane fusion, the clathrin-independent and dependent endocytosis fascinate SARS-CoV entry too (53,54). Following the virus entrance within the cells, the viral RNA genome let out within the cytoplasm and decode into structural protein and tow polyprotein, afterwards the genome of virus initiates duplication and replication (34). The afresh designed enveloped glycoprotein are intersected within the membrane of Golgi or ER (endoplasmic reticulum), and the nucleocapsid is molded by the blend of genomic RNA and nucleocapsid protein. Afterwards, the particles of virus shoot-up at the Endoplasmic reticulum-Golgi intermediate compartment (ERGIC) (35). At last, the virus particles contained by vesicles start fusing with the plasma membrane to discharge the virus (39).

Presentation of coronavirus antigen

After the virus enters into the cell, an antigen is offered to the antigen presentation cells (APC), this one has a fundamental role in the anti-viral immunity of the body. Antigen peptides being accessible by human leukocyte antigen (HLA) or major histocompatibility complex (MHC) recognized by virus-specific cytotoxic T lymphocytes (CTLs) in humans (35). Therefore, knowledge of antigen presentation in SARS-CoV-2 is must for the better understanding the nCOVID-19 pathogenesis. Although, SARS-CoV antigen presentation mainly depends on MHC I (55) molecule but MHC II also contributes to its presentation. Earlier reports suggested the SARS-CoV susceptibility correlates with HLA polymorphism such as HLA-B*4601, HLA-B*0703, HLA-DR B1*1202, HLA-B*4601, HLA-B*0703 (56) and HLA-CW*0801 (57), however the HLA-DR0301, HLA-A*0201 and HLA-CW1502 alleles, on the other hand, provides protection from SARS infection (58). During MERS-CoV infection susceptibility to infection is associated with Major Histocompatibility Complex II (MHC II) like HLA-DRB1*11:01 and HLA-DQB1*02:0 (59). Likewise, gene polymorphisms of MBL (mannose-binding lectin) associated with antigen presentation are correlated to higher SARS-CoV infection risk (60). Such pieces of information

would deliver high beneficial evidences for the mechanism and treatment of nCOVID-19.

Evasion of immune surveillance

SARS-CoV and MERS-CoV sustain in host cells by using multiple approaches by avoiding immune response. An evolutionary conserved microbial structure called pathogen-associated molecular patterns (PAMPs) can be recognized by pattern recognition receptors (PRRs) (35). However, SARS-CoV and MERS-CoV can persuade double-membrane vesicles production then replicates in these vesicles that lack PRRs, thus avoiding the host detection of their dsRNA (61). IFN-β (IFN-I) and IFN-α provide shielding effects on SARS-CoV and MERS-CoV but in an infected mouse, IFN-I pathway is inhibited (62,63). MERS-CoV, accessory protein 4a may chunk the induction of interferon at the level of MDA5 activation through interaction with double-stranded RNA (64). In addition to membrane proteins of MERS-CoV and ORF5, ORF4a, ORF4b inhibit nuclear transport of interferon regulatory factor 3 (IRF3) and stimulation of interferon β (IFN β) promoter (65). Coronavirus also affects the antigen presentation like gene expression related antigen presentation is down-regulated after MERS-CoV infection (66). Thus, smashing the immune evasion of SARS-CoV-2 is very crucial for the effective treatment against the virus.

Cytokine storm

Interestingly, B and T lymphocytes (Immune cells), bone marrow, thymus, spleen and macrophages are negative for ACE2 (28,46). These detections suggest that the patients suffering from Coronavirus may be treated with immunological therapy, however when the patient's own over activated immune system kills the virus, it generates inflammatory factors in larger number subsequently lead to cytokine storm (28,37). The deadly uncontrollable inflammatory response results in releasing of a terrible amount of pro-inflammatory cytokines (IFN-α, IFN-γ, TNF-α, TGF-β, IL-33, IL-18, IL-12, IL-6, IL-1β, etc.) and Chemokines (CXCL10, CXCL9, CXCL8, CCL5, CCL3, CCL2, etc.) in the lungs through immune effector cells in SARS-CoV infection (28,37,67-69). Similarly, infection MERS-CoV showed higher levels of IL-6, IFN-α, IL-6, CCL5, CXCL8, CXCL10 in diseased patients (70). Therefore, sidestepping the cytokine storm maybe crucial for treating nCOVID-19 diseased patients as the cytokine storm stimulate attack by the body's own immune system that further cause acute respiratory distress syndrome, cardiac arrest, dysfunction of the air exchange and MOD, which finally leads to death in nCOVID-19 infection just like in SARS-CoV and MERS-CoV infection (28,37,40).

Response of humoral and cellular immunity

Cellular and humoral immunity in the body stimulate by the antigen presentation subsequently, which is driven through a virus specific T cells and B cells. Likewise, to other acute viral infection, the AB (antibody) profiles against SARS-CoV produces the typical IgM and IgG pattern (35). The SARS specific IgG antibody may last for a longer time as compared to IgG antibody which usually disappears by the end of 12 weeks, thus it may be concluded that IgG antibody plays a protective role against the virus (71). Many publications on such areas are more concerned about the cellular immunity comparing to humoral response against coronavirus study (35). The study by (72) demonstrated that number of CD8+ and CD4+ T cells in the SARS-CoV-2 diseased patient peripheral blood is reduced significantly, while its status activated, as evinced by a higher proportion of CD38 (CD8, 39.4%) HLA-DR (CD4, 3.47%) (73). Also, the acute phase response in SARS-CoV patients is indicated with decreased CD4+ and CD8+ T cells. Even, in case of no antigen, CD4+ and CD8+ memory T cells can stay for up to almost 4 years in a part of SARS-CoV recovered individuals and can perform proliferation of T cells, production of IFN-γ and DTH response (71). Six years after SARS-CoV infection, specific T-cells memory responses to the SARS-CoV S peptide library could still be identified in 14 of 23 recovered SARS-CoV patients (35,74). The specified CD8+ T cells turned up showing akin event on MERS-CoV clearance in mice (75). This piece of information may prove valuable for working on the therapy aspects of nCOVID-19.

Management of nCOVID-19

Approximately 90 vaccines are being developed to fight against nCOVID-19 by research corporates and universities around the globe (76,77). Scientists are trialing and validating several technologies, some of which have not been used in licensed treatment/vaccination before. A study (76) grouped a few vaccines like Virus vaccines, Nucleic-acid vaccines, Protein-based vaccines, and Viral-vector vaccines, that have already started injecting into volunteers for safety trials and some for-animal studies (76).

Mesenchymal SCs transplantation can improve the outcomes in patients suffering from nCOVID-19 related symptoms. Parallelly, the Italian College of Anesthesia, Analgesia, Resuscitation, and Intensive care have issued certain guidelines to treat nCOVID-19 diseased cases (47), by indicating the declaration of the key potentiality of stem cells to relief the nCOVID-19 patients quickly (47).

Immunological therapy may be considered as one of the potential treatment but the immunomodulatory capacity can't stand strong alone in case of only or two immune factors will be considered because the virus has the ability to stimulate cytokine storm in the lungs itself, which further lead to acute respiratory distress syndrome (ARDS), multi-organ failure, cardiac arrest, and other infection which results into deadly outcomes (28,37). Therefore, avoiding/evading cytokine storm is better while treating nCOVID-19 infected population which also mean immunological therapies may not be sufficient to fight against the deadly virus (28,31). However, 'Master Cells' or stem cells like MSCs have the intrinsic powerful immunomodulatory ability and carry the advantage for attenuating cytokine Storm and thereby beneficial as a therapy to treat nCOVID-19 infected patients (27,28,31).

Cell-therapies are leading the biomedical research ranging from tissue engineering to regenerative medicine and incorporated in curing a number of diseases including cardiovascular (78-80), pulmonary (81-84), renal (85-87) etc. On the other hand, despite numerous literatures stating the immunomodulatory or regenerative effect of stem cell-based therapies, federal trade commission (FTC) issued legal lawsuit against stem cell-based therapy in clinical practices (88). Throughout the controversial background of stem cell-based therapy, Food and Drug Administration (FDA) have considered multiple clinical trials of stem cell therapy and issued new guidance and clearance before practicing the therapy on the roadway of the clinic (89-95). The deadly virus infection and spread has assembled researchers and clinicians from different life sciences branches to find a treatment or the solution towards the ongoing worst pandemic of this century. International Society for Stem Cell Research (ISSCR) has recently announced that presently there is no approved stem cell-based therapy for treating and preventing of coronavirus infection (27). However, just as the other multiple treatment strategies are into the pipeline, MSCs have been introduced as a potential therapeutic approach to deal and manage the treatment associated with deadly nCOVID-19 (96).

After the nCOVID-19 disaster, many researchers around the globe combine the stem cell infusion for treating COVID mobility and mortality, one such study was published in China on a stem cell based clinical trial that improved the critical case of 65 years old Chinese women suffering from nCOVID-19 after the infusion of MSCs (97). After this publication published in the scientific market, many clinical stem cell trials have been started since date, another report from Beijing responded positive outcomes on treating seven nCOVID-19 patients with stem cell therapy (28). WHO has also created the central database around the globe running stem cell clinical trials to treat the deadly virus nCOVID-19. Finally, in February 2020, Director of Biological Technology, Ministry of Science and Technology in Beijing, Mr. Zhang Xinmin, during a press conference, announced the safety and effectiveness of stem cell-based therapy based on preliminary experimental results running across the country (98).

Role of hMSCs in coronavirus pandemic

hMSCs have been used frequency from basic regenerative, translation research to human clinical trials (28,99,100). MSCs safety and effectiveness have already been clearly recognized in numerous clinical trial studies like in Graft-versus-host disease (GVHD) (101) or Systematic lupus erythematosus (SLE) (102). After the nCOVID-19 infection, the body tends to accelerate the immune overreaction which further produces a large number of inflammatory factors, thus initiating cytokine storm with an overproduction of immune cells and cytokines (103). Here, comes the role of Corona warrior, i.e., the MSC therapy for treating nCOVID-19 patients. Mesenchymal SCs shows a key and lead role primarily into two different ways, their differentiation abilities and immunomodulatory effects (27,28,31). At a cellular level, Mesenchymal SCs itself contains some natural immunity towards the coronavirus due to their powerful immunomodulatory capability. Mesenchymal SCs have valuable effects in preventing or attenuating the cytokine storm simply by secreting anti-inflammatory factors (31) by paracrine secretion (28). Mesenchymal SCs with the ability of paracrine secretion may secrete many types of cytokines or make direct interaction with certain immune cells like T cells, B cells, macrophages, natural killer cells and dendrite cells (31) The Mesenchymal SCs immunomodulatory effect is further triggered by the stimulation of TLR receptor in Mesenchymal SCs, which is stimulated by pathogen-associated molecules such as novel coronavirus double-

stranded RNA or LPS (104,105). Mesenchymal SC therapy inhibits the overreaction by the immune system and thereby encourage endogenous repair, i.e., reparative trait of SCs by improving the microenvironment (27,31). After intravenous injection of MSCs, some part of Mesenchymal SCs entraps within the lungs, which further improves the pulmonary microenvironment by protecting alveolar epithelial cells, prevent pulmonary fibrosis and improve overall lung dysfunction and nCOVID-19 associated pneumonia (28,82,83). MSCs have also stand-up superior in improving functions related to cardiovascular, hepatic, renal, acute respiratory syndrome and multiple other disorders (85,106).

Therefore, it can be stated that MSCs based therapy may possibly play a key and warrior role for clinical trial in combination with conventional treatment to explore the therapeutic potential to treat nCOVID-19 infected patients (28).

Challenges and future prospects

MSCs have in many of the clinical and preclinical trials have shown promising results in conditions of inflammatory airway disorders and other immune disorders. This has led the researchers to plan and conduct clinical trials to combat the nCOVID-19 pandemic, as the major symptoms of an attack are related to inflammatory airway disorders. Though we have many questions in mind, the need of the hour is to find out a solution for this pandemic and hence no stone should be left unturned, which may lead us in mitigating the symptoms of the disease. MSCs derived from different tissue sources show many similarities and they also exhibit obvious differences in their properties and this is a very important point which should be kept in consideration.

In one the of the study performed by Yang *et al.* in 2013 (107), Biological and phenotypic characteristics of different MSCs sources were compared, sources included were adipose-MSCs, bone marrow-MSCs, umbilical cord-MSCs and chorionic villi-MSCs. The results have demonstrated CD106+ (VCAM-1) was highly expressed in chorionic villi-MSCs, fairly on bone marrow-MSCs, and very light expression was observed on umbilical cord-MSCs, however, the expression was absent on adipose-MSCs. The CD106+ cells have shown to be more efficient in the modulation of T helper subsets (107). Umbilical based MSCs and Wharton Jelly based MSCs are also being used in managing critically ill nCOVID-19 Patients have been suggested by some of the research groups in the UK and China (31,108-110).

These are some hope inducing studies wherein it has been shown that the management of the nCOVID-19 cases is possible with cell-based therapy. However, there are several questions which need to be answered. Many more randomized and multicentric clinical trials will throw more light into this domain. With such clinical trials and exchange of data, we may narrow down the type of stem cells, dose, route of injection and follow-up interventions requirement (111,112).

Apart from these, there are many more questions which need to be answered. As many of the studies are using the cultured MSCs, we need to understand and compare the culture condition of the different laboratories. Which are the signaling pathway modulated by these cells? Where exactly in the signaling pathway cytokines secreted by MSCs act? How theses MSCs infusion will affect an nCOVID-19 patient having comorbidity? How the safety regulations of the previous trials will pave the way for a more safe and effective treatment? (113).

We will be able to make these trials, even more, useful and meaningful, if we try to find out the answer to these questions and many more which we may not have thought. More and more cooperation in research and developments is required to combat this pandemic and the better and free exchange of results, findings need to be shared among the affected countries, to mount a good attack on the virus.

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Footnote

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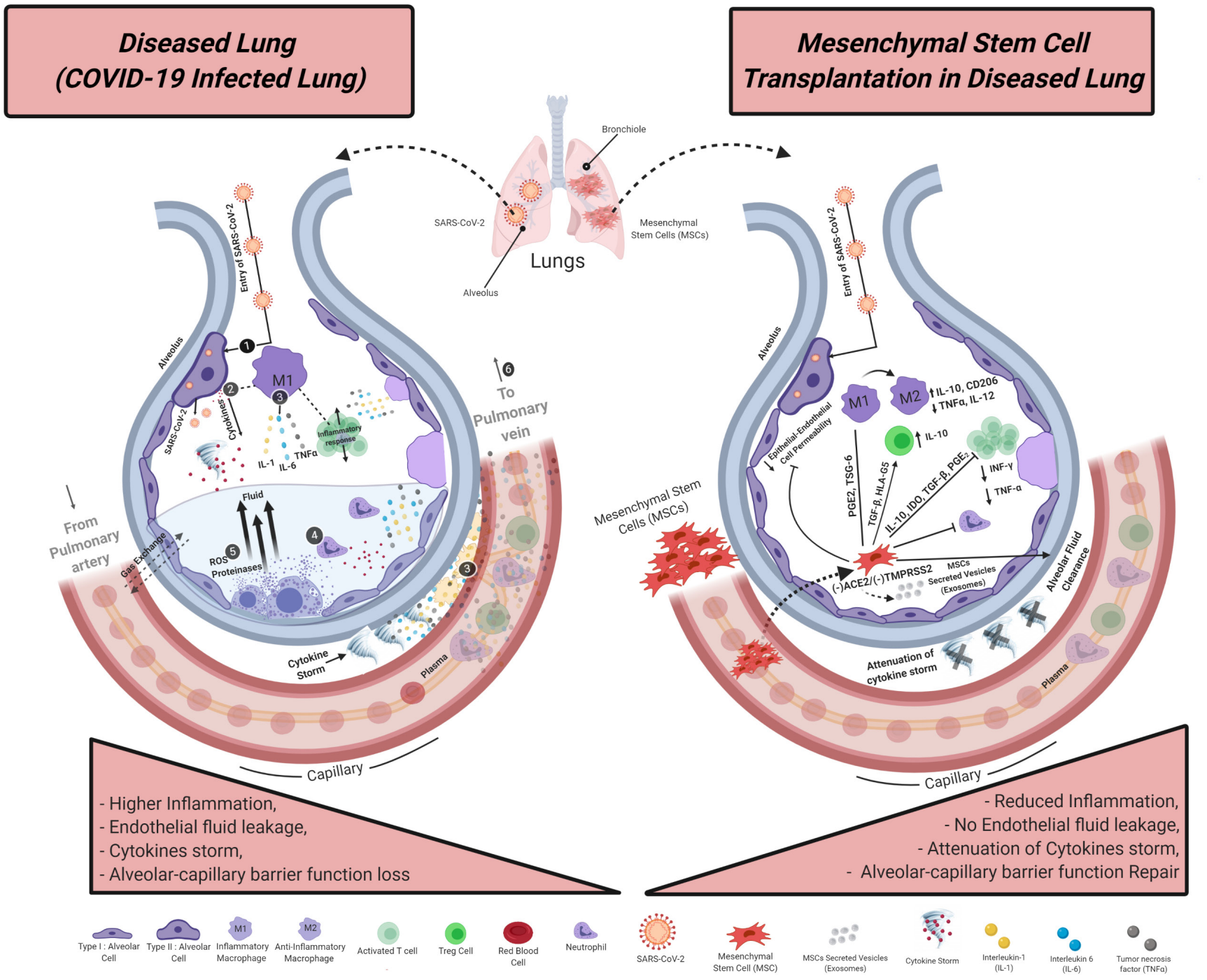

Figure S1 Diseased lung (COVID-19 infected lung): (I) when the SARS-CoV-2 enters the alveolus, it starts to infect the alveolar type II cells and replicates, (II) the alveolar type II infected cells tend to release pro-inflammatory cytokines, which further signals the body's immune system to respond, which leads to mild symptoms like cough, body ache and fever in COVID-19 infected patients, (III) IL-1, IL-6 and TNF-α released by macrophages causes vasodilation which permits more immune cells to travel to the alveolus. It further causes an increase in capillary permeability, which results in the plasma leakage into the alveolus and interstitial space, (IV) parallelly, neutrophils release proteinases and reactive oxygen species (ROS), which destroy infected cells, (V) these infected or dead cells pool with the plasma to form a protein-rich fluid that remains collected within the alveolus, causing pneumonia and shortness of breath. Accumulation of fluid and dilution of surfactant lining the alveolus causes collapse of alveolar, which reduces the gas exchange and can lead to acute respiratory distress syndrome, (VI) overdrive of the immune system, causes inflammation spread throughout the circulatory system leading to cytokine storm (systemic inflammatory response syndrome), this storm can drastically drop the blood pressure (septic shock) leading to multi-organ failure or death as organs can no longer be perfused. Created with BioRender.com. Mesenchymal stem cells (MSCs) transplantation in the diseased lung: MSCs and their secreted extracellular vesicles (Exosomes) potentially modulate the immune cells (T cells and dendritic cells) and epithelial cells, which are involved in the airway inflammation. The mesenchymal SCs function their modulatory effects via promoting anti-inflammatory cytokine, chemokines, cell-cell contact, mitochondrial transfer and genomic regulation, which could attenuate inflammation and regenerate lung damage caused by nCOVID-19. It has been studies that SARS-CoV-2 can infect angiotensin I converting enzyme 2 (ACE-2) receptor-positive cells, however MSCs lack ACE-2 receptors and TMPRSS2. Thus, when SARS-CoV-2 enter and infect the alveolar type II cells, MSCs inhibits epithelial-endothelial cell permeability. Further PGE2, TSG-6 secreted by MSCs influence the macrophage switch from M1 (an inflammatory) into M2 (an anti-inflammatory) state. This MS macrophage expresses high levels of Interleukin-10 and CD206, additionally reduces Interleukin-12 and TNF-α levels, and demonstrates elevated phagocytic activity. Further MSCs support and trigger the development of Treg populations via immunomodulatory factors (TGF-β, and HLA-G5) and expresses higher Interleukin-10 level, thus collectively modulate and balance Treg. During an inflammatory environment created by activated cells, MSCs recruit effector T cells and local helper (Th). The inducible NO synthase (iNOS) and intracellular enzymes indoleamine-2,3-dioxygenase (IDO) produced by MSCs are some of the mediators of T cell suppression, that further promotes their polarity shift from a Th1 state (pro-inflammatory) to Th2 state (anti-inflammatory). Lipid mediator prostaglandin E2 (PGE2), interleukin-10 (IL-10), and transforming growth factor β (TGF-β) secretion by MSCs inhibit the production of tumor necrosis factor α (TNF-α), interferon γ (IFN-γ), and Th17 cell differentiation. MSCs secreted IL-6, diminishes respiratory burst from neutrophils, the suppression of peroxidase and protease (releasing destructive enzymes) save neutrophils from apoptosis. Thus, through the anti-inflammatory mechanism, MSCs results into an attenuation of cytokine storm, alveolar fluid clearance and maintain alveolar-capillary barrier function. Created with BioRender.com.

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