‘Primed’ Mesenchymal Stem Cells: a Potential Novel Therapeutic for COVID19 Patients

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Abstract

The COVID19 pandemic, designated as a public health crisis by the World Health Organization (WHO), is rapidly spreading around the world impacting the health and economy of almost all the countries. The data of hospitalized COVID19 patients, especially those with serious illness, indicate the involvement of immunopathological complications. As no effective treatment is currently available, we propose ‘Primed’ Mesenchymal Stem Cells (MSCs) as a therapeutic alternative to tackle devastating epidemic. The individual response to MSCs treatment is heterogeneous. During the treatment of infectious pathology, the effectiveness of the treatment may vary based on the disease scenario. Interestingly, when transplanted in vivo, MSCs are governed by the locally regulated microenvironment, suggesting that the restorative variability could be tailored by choosing a priming regimen to specifically correct a given pathology. Therefore, in our opinion, the priming of MSCs could be a novel approach to improve the responses of COVID19 patients.

Keywords COVID19 · Coronavirus · SARS-CoV-2 · Mesenchymal stem cells · MSC priming · Immunomodulation

Main

Over the past 5 months, the coronavirus disease 2019 (COVID19) pandemic has relentlessly impacted the global population. The first case of COVID19 infection was identified in the Wuhan City of China on December 1, 2019. Since then, the virus has spread to 213 countries and territories, resulting in over 5.3 million confirmed cases and over 340,000 deaths as on May 23, 2020 (https://www.worldometers.info/coronavirus/). People of all ages are vulnerable to COVID19 infection; however, those over 60 years of age and with pre-existing medical conditions, such as cardiovascular disease, diabetes, or high blood pressure, are more prone to fall seriously ill and succumb to the disease. According to the Centers for Disease Control and Prevention, the symptoms of COVID19 include fever, cough, and shortness of breath, fatigue and sudden loss of sense of smell and taste in some cases (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html), though its typical characteristic is pneumonia that requires hospitalization and even death, if not intervened timely.

For any therapeutic intervention, the pathological cascade involved in a disease needs to be elucidated. Therefore, identifying the SARS-CoV-2 virus receptor recognition mechanism that regulates its virulence and pathogenesis holds the key to confront the COVID19 epidemic [1]. Structural analysis of SARS-CoV-2 revealed that the enveloped, positive-sense, single-stranded RNA viruses belong to the genus β-coronavirus and have azoonotic origin [2]. Mounting evidence suggests that SARS-CoV-2 primarily spreads through the respiratory tract, either in the form of droplets, respiratory secretions, or direct contact [3]. In addition, the abundant presence of ACE2 protein receptor in lung alveolar epithelial cells facilitates the binding of SARS-CoV-2 spike-S-glycoprotein, and thus, expedites viral infection. This interaction also activates distinct cytokines crucial for antiviral responses. The data of critically severe COVID19 patients revealed the presence of IL-2, IL-6, IL-7, IL-10, TNF-α, GCSF, MCP-1, MIP-1α, and TNF-α [4] to name a few. To date, no specific approved antiviral therapy for the treatment of COVID19 infection is available, except standard supportive care e.g.,
oxygenation, ventilation, and fluid management, etc., and some non-specific treatments e.g., hydroxychloroquine and chloroquine etc., to ameliorate the symptoms, and some antivirals and protease inhibitors. Thus, to reverse or combat the detrimental effect produced by SARS-CoV-2 virus, there is an urgent need for a reliable therapy. In this context, multipotent mesenchymal stem cells (MSCs) have shown a strong safety and efficacy profile as they have been intensively investigated in preclinical and clinical studies of various lung diseases, including respiratory virus-induced acute respiratory distress syndrome (ARDS) [5, 6]. Over the past years, the MSCs infusion exhibited an excellent safety record as evident in the 871 clinical trials registered in the National Institute of Health database (https://clinicaltrials.gov/ct2/results?cond=Mesenchymal+Stem+Cells&term=&cntriy=&state=&city=&dist=), including 117 trials (https://clinicaltrials.gov/ct2/results?cond=mesenchymal+stem+cell&term=pulmonary&cntriy=&state=&city=&dist=&Search=Search) on pulmonary complications, to date. On the other hand, 2845 COVID19 trials worldwide as of 23 May 2020 at World Health Organization-International Clinical Trial Registry Platform (https://www.who.int/ictrp/en/) and 29 clinical trials on MSCs and COVID19 as of 23 May 2020 (https://clinicaltrials.gov/ct2/results?cond=mesenchymal+stem+cell&term=COVID19&cntriy=&state=&city=&dist=&Search=Search) have been registered at the NIH database. Worth mentioning, that out of 29 clinical trials, one has been withdrawn (trial no. NCT04293692), therefore, as yet, 28 trials have been registered with a participation of approximately 1525 patients. All of the mentioned studies that employ MSCs and COVID19 patients are in early-phase, and either recruiting or yet to recruit the participants.

To brief, out of the twenty-four clinical trials UC-MSCs will be utilized in eleven clinical trials, and AD-MSCs will be utilized in six trials, two will employ DPSCs, one with OM-MSCs, three on BM-MSC, and one (NCT04276987) will utilize exosomes derived from allogenic adipose mesenchymal stem cells, also the trial no. NCT043660663, with 60 participants, will be utilizing the MSC-derived exosomes in twenty participants (20/60), twenty will receive MSC only (20/60), and the rest twenty will be treated as control (20/60). Four registries do not reveal the tissue source (Table 1). The minimum age eligibility criteria in all the trials are 18 years, except the trial no. NCT04349631, NCT04362189, and NCT03042143 where child, adult, or aged, all are eligible to get enrolled as participants. None of the above studies have gender restriction, and the minimum follow-up time is 3 months for each of these investigations. The above registries indicate that a majority of studies will employ umbilical cord-derived MSC which seems reasonable for the following reasons: ease of harvest, fast doubling time, high scalability, and since umbilical cord has a high concentration of stem cells, they can provide a large amount of cells. Noteworthy they have faster doubling times, more plasticity, and with no tumorigenicity [7, 8]. They are derived from discarded tissue, and so have less ethical concern. In our opinion and experience, amongst the cell types used, equally desirable cell type for COVID19 patients is DPSCs, since they too appear to have similar advantages like UC-MSCs. Some of the unique advantages associated with DPSCs are noninvasive isolation, ease of harvest, and easy accessibility, as they reside in the impacted third molar; besides strong therapeutic ability are the key advantages of DPSCs [9]. They show clonogenicity, and higher ex- vivo proliferative capacity [10] compared with MSCs; they are less prone to malignancy [11], and therefore can give rise to sufficient numbers of cells for cell therapy. Compared with umbilical cord stem cells, DPSCs demonstrated delayed cellular senescence [12] which can be correlated to the increased expression of genes related to growth factors [13]. They have minimal ethical concerns, which is otherwise a hurdle often associated with other cell types. In the presence of specific stimuli, they can give rise to several cell types [14, 15]. As per our knowledge, to date, there is only a single preclinical investigation [6], apart from a case report [16] that supports the rationale for the use of MSCs in COVID19. Interestingly, the Abu Dhabi Stem Cell Center (ADSCC), UAE has recently supervised a clinical trial on 73 COVID19 patients employing ‘Activated’ MSCs. The study claims that all the participants were successfully treated and cured relieved of symptoms of the virus by inhaling the treatment into their lungs after it has been nebulized into a fine mist (https://www.khaleejtimes.com/coronaviruspandemic/coronavirus-uae-stem-cell-treatment-fights-symptoms-of-covid-19-not-cure-it–). The source of the MSCs was patients own blood. However, no further information has been provided, therefore, more detailed information regarding the procedure of stem cell processing and priming, dose and timing of MSCs inhalation, patients’ age and gender, and the follow-up is needed to determine the efficacy of MSCs activation on those patients.

Interestingly, the data obtained from a single-center, open-labeled pilot investigation in COVID19 patients from China demonstrated that the treatment with MSCs improved disease-associated parameters in severe and critically severe patients [16]. To brief, seven patients (one critically severe, four severe, and two having common symptoms of pneumonia) were enrolled in the treatment group, where as three patients served as placebo controls (all displaying severe symptoms). All treated patients received a single dose of 1X10^8 MSCs/kg body weight. Remarkably, all seven showed improvement over two weeks with no noticeable adverse effect, thereby, demonstrated the safe and effective infusion of ACE2-ve MSCs in COVID19 pneumonia patients. The overall improvement in the MSCs infused group was striking as within 2 days after treatment pulmonary functions and symptoms of all the seven patients significantly improved, and most tested...
| S.No. | Clinical trial number | Study Title                                                                 | Phase | Status               | Sample Size (n) | Cellular Interventions | Date of Start (DOS) | Date of Completion (DOC) | Gender | Age            | Country |
|-------|-----------------------|------------------------------------------------------------------------------|-------|----------------------|-----------------|------------------------|---------------------|-------------------------|--------|----------------|---------|
| 1     | NCT04315987           | Nest Cell®Mesenchymal Stem Cell to Treat Patients with Severe COVID19 Pneumonia | I     | Not Recruiting       | 66              | Nest Cell®            | DOS: April 2020      | DOC: June 2020          | Both   | 18 Yrs. and older | Brazil  |
| 2     | NCT04313322           | Treatment of COVID19 Patients Using Wharton’s Jelly- Mesenchymal Stem Cells   | I     | Recruiting           | 5               | WJ-MSCs               | DOS: March 2020      | DOC: September 2020     | Both   | 18 Yrs. and older | Jordan  |
| 3     | NCT04288102           | Treatment With Mesenchymal Stem Cells for Severe Corona Virus Diseases 2019 (COVID19) | II    | Recruiting           | 90              | MSCs                   | DOS: March 2020      | DOC: July 2020          | Both   | 18 to 75 Yrs. | China   |
| 4     | NCT04302519           | Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells Early phase | Not Recruiting | 24               | DPSCs           | DOS: March 2020      | DOC: July 2020        | Both   | 18 to 75 Yrs. | –       |
| 5     | NCT04252118           | Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With 2019 Novel Coronavirus | I     | Recruiting           | 20              | MSCs                   | DOS: January 2020    | DOC: December 2021     | Both   | 18 to 70 Yrs. | China   |
| 6     | NCT04273646           | Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Novel Coronavirus Severe Pneumonia | –     | Not Recruiting       | 48              | UC-MSCs               | DOS: April 2020      | DOC: February 2022     | Both   | 18 to 65 Yrs. | China   |
| 7     | NCT04276987           | A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia | I     | Not Recruiting       | 30              | Exosomes derived from AD-MSCs (MSC-Exo) | DOS: February 2020 | DOC: July 2020          | Both   | 18 to 75 Yrs. | –       |
| 8     | NCT04336,254          | Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID19 Patients | I and II | Recruiting            | 20              | DPSCs                  | DOS: April 2020      | DOC: March 2021         | Both   | 18 to 65 Yrs. | China   |
| 9     | NCT04339,660          | Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID19 Pneumonia | I and II | Recruiting            | 30              | UC-MSCs               | DOS: February 2020   | DOC: June 2020          | Both   | 18 to 75 Yrs. | China   |
| 10    | NCT04346,368          | Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID19) | I and II | Not Recruiting       | 20              | BM-MSCs               | DOS: April 2020      | DOC: December 2020     | Both   | 18 to 75 Yrs. | China   |
| 11    | NCT04352,803          | Adipose Mesenchymal Cells for Abatement of | I     | Not Recruiting       | 20              | AD-MSCs               | DOS: April 2020      | DOC: April 2026        | Both   | 18 to 90 Yrs. | –       |
| S.No. | Clinical trial number | Study Title | Phase | Status | Sample Size(n) | Cellular Interventions | Date of Start (DOS) | Gender | Age | Country |
|-------|-----------------------|-------------|-------|--------|----------------|------------------------|---------------------|--------|-----|---------|
| 12-   | NCT043 49,631         | A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Autologous Mesenchymal Stem Cell Therapy (HBadMSCs) to Provide Protection Against COVID19 | II    | Enrolling by invitation | 56 | AD-MSCs | DOS: May 2020 DOC: December 2020 | Both | Child, Adult, Older Adult | United States |
| 13-   | NCT030 42,143         | Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST) (COVID19) (REALIST) | I and II | Recruiting | 75 | UC derived CD362 enriched MSCs | DOS: January 2019 DOC: October 2022 | Both | 16 Yrs. and older | United Kingdom |
| 14-   | NCT043 90,152         | Safety and Efficacy of Intravenous Wharton’s Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome due to COVID19 | I and II | Not Recruiting | 40 | WJ-MSCs | DOS: June 2020 DOC: May 2021 | Both | 18 to 80 Yrs. | Colombia |
| 15-   | NCT043 82,547         | Treatment of COVID19 Associated Pneumonia with Allogenic Pooled Olfactory Mucosal derived Mesenchymal Stem Cells | I and II | Not Recruiting | 40 | OM-MSCs | DOS: May 2020 DOC: June 2021 | Both | 18 to 70 Yrs. | Belarus |
| 16-   | NCT043 66,323         | Clinical Trial to Assess the Safety and Efficacy of Intravenous Administration of Allogeneic Adult Mesenchymal Stem Cells of Expanded | I and II | Not Recruiting | 26 | AD-MSCs | DOS: April 2020 DOC: October 2021 | Both | 18 to 80 Yrs. | – |
| S.No. | Clinical trial number | Study Title                                                                 | Phase | Status                  | Sample Size (n) | Cellular Interventions                          | Date of Start (DOS) | Date of Completion (DOC) | Gender          | Age                | Country   |
|-------|-----------------------|------------------------------------------------------------------------------|-------|-------------------------|-----------------|---------------------------------------------------------------------------------|---------------------|--------------------------|----------------|-------------------|-----------|
| 17-   | NCT043 66,063         | Adipose Tissue in Patients with Severe Pneumonia due to COVID19              | II    | Recruiting              | 60              | MSCs, and Exosomes derived from MSCs (MSCs-Exo)                               | DOS: April 2020     | DOC: December 2020        | Both            | Iran              | Iran      |
| 18-   | NCT043 77,334         | Mesenchymal Stem Cells (MSCs) in Inflammation-Resolution Programs of Coronavirus Disease 2019 (COVID19) Induced Acute Respiratory Distress Syndrome (ARDS) | II    | Not Recruiting          | 40              | BM-MSCs                                                                     | DOS: May 2020       | DOC: February 2021        | Both            | 18 Yrs. and older | Germany  |
| 19-   | NCT043 71,393         | MSCs in COVID19 ARDS                                                        | III   | Recruiting              | 300             | MSCs Remestemcel-L                                                           | DOS: April 30, 2020 | DOC: April 2022           | Both            | United States       | United States |
| 20-   | NCT043 62,189         | Efficacy and Safety Study of Allogeneic HB-adMSCs for the Treatment of COVID19 | II    | Not Recruiting          | 110             | AD-MSCs                                                                     | DOS: May 2020       | DOC: October 2020         | Both            | Child, Adult, Older Adult | United States |
| 21-   | NCT043 66,271         | Clinical Trial of Allogeneic Mesenchymal Cells from Umbilical Cord Tissue in Patients with COVID19 | II    | Recruiting              | 106             | UC-MSCs                                                                     | DOS: May 2020       | DOC: May 2021             | Both            | Spain             | Spain     |
| 22-   | NCT043 48,435         | A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Allogeneic Mesenchymal Stem Cell Therapy (HBadMSCs) to Provide Protection Against COVID19 | II    | Enrolling by invitation | 100             | AD-MSCs                                                                     | DOS: April 2020     | DOC: April 2021           | Both            | Child, Adult, Older Adult | United States |
| 23-   | NCT043 71,601         | Safety and Effectiveness of Mesenchymal Stem                                   | Early Phase I | Recruiting         | 60              | UC-MSCs                                                                     | DOS: March 2020     | Both                      | 18 to 70 Yrs. | China             | China     |
| S.No. | Clinical trial number | Study Title | Phase | Status | Sample Size (n) | Cellular Interventions | Date of Start (DOS) | Date of Completion (DOC) | Gender (Male/Female/Both) | Age | Country |
|-------|-----------------------|-------------|-------|--------|-----------------|------------------------|-------------------|--------------------------|--------------------------|-----|---------|
| 24-   | NCT043 55,728         | Use of UC-MSCs for COVID19 Patients | I and II Recruiting | 24 | UC-MSCs | DOS: April 2020 DOC: May 2021 | Both | 18 Yrs. and older United States |
| 25-   | NCT043 92,778         | Clinical Use of Stem Cells for the Treatment of COVID19 | I and II Recruiting | 30 | UC-MSCs | DOS: April 2020 DOC: September 2020 | Both | 40 to 60 Yrs. Turkey |
| 26-   | NCT043 97,796         | Study of the Safety of Therapeutic Tx with Immunomodulatory MSC in Adults with COVID19 Infection Requiring Mechanical Ventilation | I Not Recruiting | 45 | BM-MSCs | DOS: June 2020 DOC: June 2021 | Both | 18 to 80 Yrs. – |
| 27-   | NCT043 90,139         | Efficacy and Safety Evaluation of Mesenchymal Stem Cells for the Treatment of Patients with Respiratory Distress to COVID19 | I and II Recruiting | 30 | WJ-MSCs | DOS: May 2020 DOC: December 2020 | Both | 18 to 75 Yrs. Spain |
| 28-   | NCT042 69,525         | Umbilical Cord (UC)-Derived Mesenchymal Stem Cells (MSCs) Treatment for the 2019-novel Coronavirus (nCOV) Pneumonia | II Recruiting | 10 | UC-MSCs | DOS: February 2020 DOC: September 2020 | Both | 18 to 75 Yrs. China |
negative for the SARS-CoV-2 nucleic acid test over two weeks after MSCs infusion. After 6 days of infusion, the therapy inhibited the over-activation of the immune system by inhibiting CXCR3+CD4+ T cells, CXCR3+CD8+ T cells, and CXCR3+ NK cells. It also decreased TNF-α and enhanced the number of peripheral lymphocytes, CD14+CD11c+CD11bmid regulatory DC, and anti-inflammatory cytokine IL-10. Moreover, the gene expression profile revealed that MSC was ACE2ve and TMPRSS2ve, which indicates that the MSCs would not be susceptible to SARS-CoV2 infection. Finally, the RNA sequencing and gene expression analysis showed that MSCs were closely involved in the anti-viral pathways, and had anti-inflammatory trophic activities [6]. In line with above findings, the results from a case report on COVID19 [16] and a study on influenza virus H9NA [5], which shares complications similar to COVID19 like ARDS and lung failure, demonstrated that MSCs can offer therapy for virally-induced pulmonary complications in clinical settings. While all these studies have provided new insights into the protective mechanism of MSCs during viral infection, a few short comings were noticed in these treatments. For example, similar to study conducted by ADSCC, there is also a lack of information on MSCs processing and screening before infusion, and the long-term follow-up of patients etc. For a protocol to be implicated in a larger cohort, optimal information regarding MSCs as well as patients needs to be investigated in a rationally designed controlled setting. Concerning the underlying mechanism by which MSCs exert a beneficial effect, the ability to home [17], engraft [17] and transdifferentiate into the target tissue, which is the infected lung in the present case, besides the bystander effect and immunomodulatory potential [9, 18, 19], are well documented. Also, the anti-apoptotic, anti-viral, and anti-bacterial functions of this therapy have been well known [20]. Under homeostatic conditions, MSCs are hypo-immunogenic and have immune evasion capabilities [21], indicating their suitability for allogeneic transplantation.

Despite years of success in MSC research, some of the challenges faced for successful transplantation therapy include heterogeneous treatment response, low number, and source-specific immunomodulatory response [22]. Interestingly, the reparative effects noticed in vivo indicate that clinical efficacy depends on the microenvironment of the transplants [23]. Therefore, the therapeutic capability of MSCs can be regulated and is an attractive area for investigation. However, resting stage MSCs do not show the above potentials; it is only when they are exposed to a stimuli milieu, they demonstrate immunomodulatory or homing potentials [24, 25]. This indicates that the modulatory activity is not constitutively expressed by MSCs but is determined by the process of ‘priming’ to be obtained. Therefore, the empowerment of MSCs by priming before a clinical application may be a potential solution to overcome the challenges that hinder the effectiveness of MSC outcomes. Priming, with inflammatory cytokines, is a process to modulate biological, biochemical or biophysical features that can influence cell fate [26, 27]. In recent years, several approaches have been proposed to improve the effectiveness, endurance and therapeutic efficiency of MSCs [28, 29]. Worth mentioning, the approaches utilizing MSCs, and especially the primed MSCs, could be vital for the success of cell therapy in lung complications, as the intravenously infused MSCs often get trapped in the lung; however, the retention time of MSCs within the lung is extremely short [30]. Though, the alteration in holding capacity of lung in a diseased scenario cannot be ruled out. As primed MSCs could efficiently enhance retention [31], beside intensifying homing [17], and survival [32] in damaged lung, therefore, activation via priming could be a crucial mechanism for retention and engraftment of MSCs in a diseased lung, subsequently providing benefits to the lung through multiple mechanisms.

Primming perspectives and MSCs robustness are currently under development. Pre-treating MSCs before injection may enhance the expression of fitness markers and stimulate greater therapeutic outcome. For instance, reports suggest cytokine mediated activation of MSCs lead to strong immunosuppressive behavior, and thereby attenuation of lung injury in rodents [31, 33], however some contradictory findings are also available as no effective role of proinflammatory cytokine priming was observed on MSCs in a model of acute lung injury and ARDS [34]. Therefore, the effect of cytokine priming needs to be further verified to prove the efficacy of primed MSCs in lung anomalies. Besides cytokines, priming of MSCs by growth factors is also a potent mechanism for MSC activation before infusion in pulmonary diseases [35]. Likewise, hypoxia preconditioning can also improve the proliferation and therapeutic efficacy of MSCs, as evident in bleomycin-induced pulmonary fibrosis model [36]. Further, employing pharmacological agents such as paclitaxel to prime MSCs could also be helpful in improving lung anomalies [37]. Therefore, in line with above findings it could reasonably by presume that MSC priming is a significant approach for treating pulmonary anomalies. In the light of above findings, herein, we propose that the mechanism of priming of MSC could be implied to the following: i) Licensing by pro-inflammatory cytokines such as IFN-γ, TNF-α, etc., to enhance immunosuppressive potential; ii) Priming by non-cytokines stimuli such as hormones/growth factors like HGF to boost defensive and protective cellular mechanisms; iii) Pre-conditioning by hypoxia, and/or pharmacological agents, e.g., sphingosine-1-phosphate, etc., to enhance engraftment and reparative effects; iv) Activation by spheroid culturing to enhance homing, survival, differentiation, and lineage specificity e.g. angiogenic mechanism; v) The timing of MSCs engraftment and engagement in the process of activation of immune cells to achieve the most excellent beneficial effect of MSCs infusion.
Nevertheless, there are several limitations associated with the priming approaches that may jeopardize MSC based therapies at clinics; hence these challenges must be overcome to harness the true potential of MSCs. For instance, the priming of MSCs by proinflammatory cytokines may negatively affect the MHC class I and class II level; Hormones and/or growth factors may affect the differentiation capacity of MSCs; Priming by hypoxia may induce oxidative stress in MSCs; Growth factors may negatively affect the differentiation capacity of MSCs; Spheroid cultures owing to the variability in their size may lead to the necrotic spheroid core, thus, may interfere with the effectiveness of MSCs after transplantation. Further, the variations in results due to the heterogeneous nature of MSCs [23], and high cost associated with priming protocols, etc., are the considerable hindrances in the successful translation of primed MSCs to the clinic. For instance, not all the priming stimulus, even the same stimuli, shows a similar effect on the cells. Therefore, the effect of individual licensing stimuli should be accessed before being employed at a manufacturing scale. For example, IFN-γ can inhibit T cell proliferation in the regulation of MSC-mediated immunosuppression [38] and can also increase the capacity of MSCs to produce different subtypes of Tregs [39]. IFN-γ can also promote increased expressions of VCAM-1 and ICAM-1 on the surface of MSCs [40]. Similarly, the adjustment of MSC infusion timing may reveal the accurate description of inflammatory surroundings related to a specific disease [41]. This may also explain why MSCs do not always exhibit beneficial effects, even in the same disease. Therefore, it is of great importance to choose the right stimuli in the right dose at and for the right timing, besides fitness of MSCs, fresh vs. cryopreserved, MSCs passage number, and route of delivery to assure homogenous clinical outcomes (Fig. 1).

To conclude, since its emergence, COVID19 has turned out to be the top priority of the healthcare system. Although stem cell treatment has not yet been proven to eliminate coronavirus completely, preliminary results are promising, suggesting that the diseased patients, under the treatment, might be more amenable to survive the infection. The effect of priming on MSCs’ therapeutic potential has been extensively researched and continues to be investigated. The results of such efforts are eagerly anticipated, as these will pave a way for a strong foundation for future scientific research and clinical applications for a variety of diseases including pulmonary complications. Finally, bearing in mind the desires for mitigation of the existing pandemic, the effectiveness of MSCs in virally infected acute respiratory diseases symptoms, and the pieces of evidence from priming strategies for MSCs, we hypothesize that endorsing priming may enhance the effectiveness of MSCs for long-term benefits which is a prerequisite for the success of stem cell therapy in COVID19 patients.

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Fig. 1 Schematic of SARS-CoV-2 infecting lung epithelial cells, and priming approaches to improve MSCs therapeutic efficacy for the treatment of COVID19 patients. (a) Represent a few priming approaches (priming by inflammatory cytokines and LPS, hypoxia pre-conditioning, (b) Primed MSCs, (c) SARS-CoV-2 and ‘Primed MSCs’ post-infusion in the lung, (d) Therapeutic effect exerted by MSCs (immunosuppression, reparative, angiogenesis, homing, anti-apoptotic, and anti-microbial activities)
Abbreviations  IL-2, interleukin 2; IL-6, interleukin 6; IL-7, interleukin 7; IL-10, interleukin 10; IFN-γ, Interferon gamma; TNF-α, Tumor Necrosis Factor alpha; MCP-1, Monocyte Chemotactic Protein 1; MIP-1α, Macrophage Inflammatory Proteins 1 alpha; GCSF, Granulocyte Colony Stimulating Factor; VCAM-1, Vascular Cell Adhesion Molecule-1; ICAM-1, Intracellular Adhesion Molecule-1; HGF, Hepatocyte growth factor; BM-MSC, Bone Marrow derived Mesenchymal Stem Cell; AD-MSC, Adipose derived Mesenchymal Stem Cell; HGF, Hepatocyte growth factor; BM-MSC, Bone Marrow derived Mesenchymal Stem Cell; DC-MSC, Dendritic Cell derived Mesenchymal Stem Cell; OM-MSC, Olfactory Mucosa derived Mesenchymal Stem Cell; DPSC, Dental Pulp Stem Cell; NK Cells, Natural Killer Cells; DC, Dendritic Cells

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