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VIEW POINTS

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Stem cell therapies for COVID-19: Strategy and application

Radbod Darabi[1] | **Yong Li**[2]

[1]McGovern Medical School, Center for Stem Cell and Regenerative Medicine, The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases, University of Texas Health Science Center at Houston, Houston, Texas

[2]Department of Orthopaedic Surgery, Western Michigan University Homer Stryker M. D. School of Medicine, Kalamazoo, Michigan

Correspondence
Radbod Darabi, McGovern Medical School, Center for Stem Cell and Regenerative Medicine, The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases, 1825 Pressler Street SRB 630C, Houston, TX 77030-3725.
Email: radbod.darabi@uth.tmc.edu

Yong Li, Department of Orthopaedic Surgery, Western Michigan University Homer Stryker M. D. School of Medicine, Kalamazoo, MI 49008.
Email: Yong.li@med.wmich.edu

Abstract

In this perspective, the potential application of stem cells for the treatment of COVID-19 related pneumonia and their potential mechanism of action have been overviewed.

KEYWORDS

COVID-19, MSCs, Stem Cell Therapy

When the novel coronavirus COVID-19 crossed over to humans in late 2019, it led to a rapid worldwide spread of the virus and developed into a devastating pandemic. As of the time of the writing of this commentary, there were more than 8.9 million confirmed cases along with an increasing number of fatalities over 468,000. This led to worldwide efforts to limit transmission, identify its pathogenic mechanisms and potential targets, and a search for druggable targets. So far, more than 2,600 clinical trials are being conducted, including many observational and interventional studies to for better understanding its pathophysiology as well as trying novel treatments. Among suggested therapeutic modalities, stem cell-based therapies have also been proposed for alleviation or treatment of COVID-19.

COVID-19 is a betacoronavirus with a positive-sense single-stranded RNA genome. Recent genome sequencing data indicates that almost 80% of the COVID-19 genome is similar to well-known members of other coronaviruses, such as SARS-CoV.[1] In addition, the virus uses the same route for adhesion and entry into human cells by adhering to the angiotensin-converting enzyme II (ACE2).[1] After cell entry, viral transcription leads to the production of polyproteins as well as other structural and nonstructural proteins such as different proteases, spikes, envelope, and nucleocapsids. These proteins have

Abbreviation: ACE, angiotensin-converting enzyme; ARDS, acute respiratory distress syndrome; CRP, C-reaction protein; IL-1, -6, -12, interleukin-1, -6, -12; MSC, mesenchymal stem cells.

important roles in virulence and pathophysiology in humans. For instance, spikes bind the virus to the host cells by adhesion into ACE2 receptors.[2] Other proteins such as the envelope are needed for virus assembly and replication in host cells. After infecting the host, the clinical presentation can vary from asymptomatic to severe cases with pneumonia (14%) and respiratory failure, which can lead to multiorgan dysfunction and septic shock.[3] Based on the recent data, the progress to severe disease and pneumonia typically happens a week after the onset of the symptoms and is manifested by dyspnea and hypoxia.

The pathogenic mechanism of pneumonia and its delayed onset is currently being studied and seems quite complex. Recent studies indicate that the development of acute respiratory distress syndrome (ARDS) in severe cases is accompanied by a massive release of proinflammatory cytokines (such as interferons and interleukins) as well as other chemokines (such as CCLs and CXCLs). This cytokine storm triggers a substantial immune response (hyperinflammation) to the affected organs leading to vascular leakage and edema, tissue inflammation/damage, multiorgan failure, and severe morbidity. Previous studies on Middle East respiratory syndrome patients similarly indicate a strong correlation between elevated serum levels of proinflammatory cytokines such as IL-6 and C-reaction protein (CRP) and disease severity. Therefore, in addition to targeted antiviral therapies, there has been a lot of attention towards immunomodulatory interventions to mitigate disease progression and severity in critically ill patients. Besides using monoclonal antibodies, such as tocilizumab and anakinra to block IL receptors or other anti-inflammatory medications, using stem cells to modify immune response have been also suggested. As mesenchymal stem cells (MSCs) are known to be immune-privileged, safe, and able to have immunomodulatory abilities, they have been tested in limited clinical trials to treat COVID-19 patients with pneumonia.

MSCs can be isolated from donor bone marrow, placenta, fat or umbilical cord and after expansion, can be administered to severe patients via the IV route to combat that cytokine storm in severe COVID patients suffering from ARDS. So far, several randomized clinical trials using MSCs (allogenic or autologous from different sources, such as bone marrow, umbilical cord, adipose tissue, etc) for COVID-19 patients are in progress worldwide. Recently, the FDA also approved their usage in severely affected COVID-19 patients under expanded access to compassionate use. The main rationale of using MSCs is based on their immunomodulatory effects by secreting different regulatory cytokines such as IL-I RA (cytokine-dependent) or their direct interaction with immune cells (cytokine-independent) and suppressing their activation or proliferation. These play key roles for polarizing regulatory T cells and monocytes/macrophages toward the anti-inflammatory phenotype.[4,5] In addition, MSC entrapment in the lung following IV injection and local secretion of cytokines and growth factors can reduce inflammation, increase alveolar macrophage phagocytosis, regulate capillary permeability, and restore alveolar fluid clearance in inflammatory lung disorders such as severe pneumonia and ARDS.[6] So far, a limited clinical trial of MSCs in seven COVID patients in China indicated their safety and possible effectiveness to treat pneumonia.[7] Improvements included reduction of CRP and tumor necrosis factor-α, increased peripheral lymphocytes and reduction of cytokine-releasing immune cells in treated patients. Further gene expression profiling of transplanted MSCs indicated their anti-inflammatory and immunomodulatory roles through secretion of a wide range of modulatory cytokines as the possible mechanism of the MSC effectiveness. Although the initial results of this study were promising, the low number of the patients (seven patients), lack of control/placebo group, and heterogeneity of the studied subjects are among major shortcomings, which warrants further research to determine the true effectiveness of MSCs for COVID-19 treatment. Except for pneumonia, other severe complications of the COVID-19 infection such as multi-organ failure and sepsis might also benefit from MSC treatment. There are several encouraging studies done on animal models of sepsis and multi-organ failure, which indicate the beneficial effects of MSC treatment in these situations (reviewed in Harok et al[8]). Possible mechanisms of actions include MSC fusion and transdifferentiation into damaged tissue, paracrine effect to inhibit cell death and tissue damage, facilitation of molecule/organelle transportation in damaged tissue, immunomodulatory effects and finally direct antimicrobial effect by secretion of antibacterial peptides (such as LL-37 or lipocalin-2) or amplification of phagocytosis. Therefore, MSCs can also be considered as an adjective therapy in complicated and end-stage COVID patients suffering from sepsis or multiorgan failure.

Aside from the acute phase of the COVID-19 disease, the recovery phase of the disease and its long-term side effects such as lung fibrosis and alveolar damage might also be another area of the interest for future stem cell therapies. Although MSCs can also be useful for reducing inflammation and consequently limiting lung fibrosis, other stem cell therapies might also be considered for eventual alveolar regeneration. For this, lung stem cells such as distal airway stem cells and alveolar epithelial type 2 cells might be a good candidate stem cell therapy for alveolar regeneration[9] in recovered patients suffering from permanent alveolar damage. These cells can be

obtained through clonal expansion or iPSC differentiation methods.

Finally, as our understanding of COVID-19 and its clinical complications increases, there is growing evidence about the involvement of other organs such as heart, liver, and neurological complications during its long clinical course.[10] These complications might also benefit from specific stem cell therapies targeting affected organs. As new stem cell therapies are emerging to treat COVID-19 patients, specific attention must be given to validate their true efficacy and possible side effects. These can be accomplished by designing appropriately controlled/randomized clinical trials and monitoring for potential side effects such as a lung/other end-organ emboli and signs of cell overgrowth/tumor formation.[11]

ORCID

Yong Li http://orcid.org/0000-0001-7956-9600

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