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JSCTT JOURNAL OF STEM CELL THERAPY AND TRANSPLANTATION
ISSN 2577-1469

Review Article

The rising role of mesenchymal stem cells in the treatment of COVID-19 infections

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Submitted: 23 June 2020
Approved: 06 July 2020
Published: 07 July 2020

How to cite this article: Al-Anazi KA, Al-Jasser AM. The rising role of mesenchymal stem cells in the treatment of COVID-19 infections. J Stem Cell Ther Transplant. 2020; 4: 011-016.

DOI: 10.29328/journal.jsctt.1001021

Infectious diseases are a leading cause of death worldwide [1,2]. The Mid-20th century witnessed most of the antimicrobial discoveries but recently there is dramatic shortage of new classes of antimicrobial agents due to failure to build a sustainable antimicrobial discovery platform [1-4]. For example, antibiotics comprise < 1.5% of the compounds under investigation at the major pharmaceutical and biotechnology companies [1,5]. Recently, the pipeline for new antimicrobials has become extremely dry as pharmaceutical companies largely withdrew in the late 1990s due to: antimicrobial therapy being less profitable than medications used to treat cancer and other chronic medical conditions; difficulty in discovering novel and efficient antimicrobials; complexity of conducting controlled clinical trials; and emergence of multidrug resistant organisms [1,6-13].

Dozens of viruses constantly infect human beings and represent sustained health and economic burden [14]. Between 1975 and 2015, > 50 new viruses that cause human disease have been described [15]. The emergence of high morbidity viruses such as: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2004, the Middle East respiratory syndrome (MERS-CoV) in 2012, and human metapneumovirus in 2001 represent global threats and highlight the importance of international collaboration on respiratory virus research [14,16]. The development of antiviral drugs is slow, complicated and full of hurdles [15]. Between 1963 and 2016, approximately 90 antiviral drugs have been approved for the treatment of several viruses including herpersviruses, hepatitis B and C viruses, and human immunodeficiency virus [15,17]. Drug resistant viral mutants which are frequently encountered in RNA viruses represent a major problem in antiviral therapy [18]. There is urgent need to control viral infections that cause human diseases particularly those caused by drug-resistant viruses [14]. Broad-spectrum antiviral agents can cover multiple viruses and reduce the likelihood of developing drug resistance [14,19]. Unfortunately, no specific antiviral drugs or vaccines are available for Coronaviridae in general [17,19].

Coronavirus disease 2019 (COVID-19) pandemic has already caused massive life losses all over the globe and has practically disturbed almost every single aspect of life and its repercussions have adversely affected world economy [20-22]. Clinically, patients with COVID-19 present predominantly with fever and respiratory manifestations but the illness may be complicated by severe pneumonia, acute respiratory distress syndrome (ARDS), and respiratory failure that may be followed by multiorgan failure and death [20,21,23-26]. The pathogenesis of COVID-19 involves: immune-mediated mechanisms; direct cytotoxicity; antibody-dependent enhancement; viral sepsis; severe pneumonia, ARDS, respiratory failure followed by multiorgan failure; and cytokine storm with significant elevation of proinflammatory cytokines [27-30]. SARS-CoV-2 infects lung alveolar epithelial cells by receptor-mediated endocytosis in association with angiotensin converting enzyme 2 (ACE-2) [31,32]. Myocardial injury associated with COVID-19 can be explained by: direct infection through ACE-2, imbalance between myocardial oxygen supply and demand, and the presence of an abnormal immune response [31-33]. In patients with COVID-19, high

levels of neutrophil extracellular traps (NETs) have been documented and the release of NETs (NETosis) may be responsible for many of the serious complications associated with COVID-19 including: ARDS, respiratory failure, cytokine storm, thromboembolic complications, and acute organ dysfunction that leads to multiorgan failure [34-37]. Leukemia inhibitory factor, which belongs to the interleukin-6 family of cytokines, could protect the lungs from further injury during pneumonia and may enhance endogenous cardiomyocyte regeneration following myocardial infarction and hence it may be useful in patients with COVID-19 pneumonia with cardiac decompensation [38,39]. In the absence of specific antiviral treatment and vaccines, the available therapeutic interventions are: symptomatic measures and supportive care including: oxygen administration, non-invasive ventilation, and mechanical ventilation; drug repurposing using mainly antiviral agents, anti-inflammatory drugs, and monoclonal antibodies; and other lines of treatment including use of convalescent plasma, removal of cytokines, Chinese traditional medicines, and mesenchymal stem cell (MSC) therapies [21,24,26,40,41].

MSCs have antimicrobial, anti-inflammatory and immunomodulatory properties and they have been used in the treatment of several infectious diseases and their complications such as ARDS both in animal models and in human clinical trials [42-49]. MSCs derived from umbilical cord blood (UCB) and adipose tissue are more advantageous than other sources of MSCs [50-55]. MSCs exhibit the following antimicrobial properties: detection and elimination of the invading pathogen by enhancing bacterial clearance; activation of the host immune response by induction of proinflammatory gradients or responses; and secretion of antimicrobial proteins [43,53,56]. MSCs have the following effects on the lungs: immunomodulatory effects; protection of alveolar epithelial cells; restoration of pulmonary microenvironment; prevention of pulmonary fibrosis; reversal of pulmonary dysfunction and control of COVID-19 pneumonia; prevention of cytokine release; and promotion of endogenous repair. Also, after intravenous (IV) administration, a significant proportion of MSCs accumulate in the lungs so a limitation can become an advantage in case of acute lung injury (ALI) or ARDS [54,57]. Additionally, MSCs have been found to modulate the functions of the following immune cells: T-cells, B-cells, natural killer cells (NKCs), dendritic cells (DCs), cytotoxic T-cells, macrophages, and neutrophils [58].

MSCs produce biologically active substances, secretomes, that are made of extracellular vesicles including exosomes, microvesicles and apoptotic bodies; soluble proteins such as cytokines, chemokines, and growth factors; lipids; nucleic acids; and conditioned media [59-64]. Advantages of secretomes include: ability to bypass the side effects of MSC-based therapy thus they are generally safer than MSCs; immediate availability for emergency use in the treatment of acute conditions; massive production from commercially available cell lines; the technical advantage of being manipulated and stored more easily than MSCs; and the lower costs compared to other therapeutic interventions such as ticilizumab [59-61]. Therapeutic effects of MSC-secretomes include: antimicrobial effects; suppression of cytokine production in ALI; enhancement of wound healing and tissue repair; anti-oxidant effects; immunomodulatory and immunosuppressive effects; regulation of angiogenesis and suppression of collagen deposition in lung tissues; as well as antitumor effects and neuroprotective effects [59-64]. After IV injection of MSC-secretome, the secretome remains highly stable in the peripheral circulation and it spreads into lung tissues to provide: immunomodulation, resolution of inflammation, restoration of capillary barrier function, and enhancement of bacterial clearance [59]. Recently it has been shown that MSCs and their secretomes have promising results in the treatment of sepsis, viral pneumonia, ALI, and ARDS thus making the secretory products of MSCs superior to pure cellular therapies [56,57,62]. MSC-secretome acts on several cytokines simultaneously and synergistically and if MSC-secretome can be formulated as a freeze-dried powder and administered as IV or by inhalation, it may represent a suitable approach for the treatment of COVID-19 pneumonia particularly in patients who are critically ill [59].

Since January 2020, several reports have been published on the success of MSC therapies in the treatment of COVID-19 complications in conjunction with other therapeutic modalities [65-68]. There are two published studies from China on the use of MSCs in the treatment of COVID-19: one included 7 patients and the second one was a single case report [65-67]. Recently, 2 commercial companies; Pluristem and Mesoblast; made press releases announcing their preliminary results on the use of MSCs in the treatment of patients having severe COVID-19 [54,69,70]. Countries such as China, the United States of America, Jordan, and Iran have begun using cellular therapies in clinical trials for the treatment of COVID-19 infections with approximately 70 registered trials, 20 of them in China. The vast majority of trials use MSCs derived from UCB and some trials are using: NKCs, embryonic stem cells, and products of MSCs such as exosomes and few of these trials use the combination of MSCs and NKCs or ruxolitinib [53,57,71]. In China, at least 4 clinical trials on the use of MSCs in the treatment of COVID-19 pneumonia, mainly using UCB-MSCs were registered in February and March 2020 [53]. Currently, MSCs are being tested in several clinical trials including: NCT04269525, NCT04288102, and NCT04252118 [57,67,71,72].

The following are required before adopting MSCs in the treatment of COVID-19 infections: updated minimal criteria for characterization of cellular therapies; updated guidelines on the use of cellular therapies in infectious diseases; updated cell therapy routines that reflect specific needs of patients requiring this form of treatment; and the use of ACE2 negative

MSCs in the treatment of patients with COVID-19 having ALI and ARDS [73-75]. In the era of COVID-19 pandemic, several groups of scientists from all over the world have recommended the use of MSCs in the treatment of severe COVID-19 infections as MSCs and their secretomes have the following beneficial effects: suppression of viral replication; enhancement of the generation of regulatory T-cells that are suppressed by COVID-19; shifting the phenotype of antigen presenting cells including DCs, B-lymphocytes, and macrophages; modulation of the proliferation and activation of naïve and effector T-cells, NKCs, and mononuclear cells; prevention of the formation of NETs; inhibition of the cytokine storm induced by COVID-19; the antiviral, antibacterial, and analgesic effects of MSC-secretomes; reduction in pulmonary edema associated with ARDS in COVID-19; entrapment of IV infused MSCs in the lungs; enhancement of tissue regeneration and promotion of endogenous repair and healing in ALI; as well as safety and efficacy of MSCs and their products provided good manufacturing practice guidelines and quality control measures are taken into consideration [8,13,34,44,52,54,73,75-86].

So, the emergence of new viruses that cause serious human infections is faced with slow and complicated antiviral drug development. In the absence of specific and curative antiviral therapy for COVID-19, plenty of medications are being repurposed with variable efficacy. MSCs and their secretomes are recommended by several groups of scientists as they can potentially control several complications of COVID-19 infections such as pneumonia, ARDS, ALI, and the associated cytokine storm.

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