Can mesenchymal stem cells be used to treat COVID-19-induced pneumonia? (Review)

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Abstract. The novel severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) which has resulted in the COVID-19 pandemic, infection by which is commonly characterized by a sore throat, fever and cough, was first reported in Wuhan, China on 31st December 2019. This novel disease is mild in certain individuals, usually younger healthy individuals, whereas the elder and those with underlying health conditions develop severe symptoms and may die as a result of the disease or associated complications. Along with pneumonia, hypercytokinemia, also termed a cytokine storm, is one of the most common pathologies observed in patients with COVID-19. As patients react to the infection with the virus differently; in certain individuals, a cytokine storm may result in death. At present, there is no cure or widely available vaccine for the novel coronavirus. However, it has been hypothesized that mesenchymal stem cells may assist in the treatment/management of the cytokine storm due to their immunomodulating properties.

Contents

1. Introduction

The COVID-19 pandemic caused by the severe acute respiratory syndrome (SARS)-CoV-2 virus, which was first reported on 31st of December in Wuhan, China, has quickly spread to 6 continents and hundreds of countries, and is the first pandemic caused by a coronavirus (CoV) (1).

CoV are a large family of viruses that can cause disease in humans and animals. They are RNA based viruses, exhibit positive polarity, and are enveloped and non-segmented, belonging to the Orthocoronavirinae subfamily (2). The total genome length of CoV is ~30 Kb. There are different regions in the genome, including a 5'-terminal noncoding region, an open reading box 1a/b-coding region, an S region encoding, a spike glycoprotein (S protein), an E region encoding the envelope protein (E protein), an M region encoding the membrane protein (M protein), an N region encoding the nucleocapsid protein (N protein) and a -3'-terminal non-coding region (3). Genomic sequence analysis of COVID-19 shows 88% similarity with two bat-derived SARS-like coronaviruses, suggesting its origins in a species other than humans (4,5).

COVID-19 may pass through mucous membranes, particularly the nasal and larynx mucosa, and then enters the lungs through the respiratory tract. SARS-CoV-2 requires the angiotensin-converting enzyme 2 (ACE2), similar to how SARS-CoV requires ACE-2 (6), as the virus appears to attack organs that express ACE2 (7-9). The first stage of pathogenesis of the virus is the identification ACE2 receptors by its spike protein. Thus, cells expressing ACE2 are likely the first cells to be infected (10). The ACE2 receptor is widely expressed on the surface of numerous types of human cells, particularly the alveolar type II cells of the lungs (11,12). Other organs which express high quantities of ACE2 receptor are the heart, liver, kidneys and digestive organs. In fact, a common cause of spread of the virus within a host is that endothelial and smooth muscle cells in almost all organs express ACE2 receptors, and thus, the virus can enter the bloodstream with relative ease. Since any tissue or organ expressing ACE2 may serve as the battlefield between the novel coronavirus and immune cells, complications such as acute respiratory distress syndrome, acute myocardial damage, arrhythmia, acute kidney injury, shock and even death may be observed (13,14). It has been reported that human-to-human transmission of SARS-CoV occurs via the binding between the receptor-binding domain of the virus spikes and cellular ACE2 receptors (5,15).

The clinical spectrum of COVID-19 symptoms varies from asymptomatic or pauci-symptomatic forms to clinical conditions, characterized by respiratory failure requiring mechanical ventilation and support in intensive care units, to

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multiorgan and systemic manifestations such as sepsis, septic shock and multiple organ dysfunction syndrome (16,17).

The aim of the present review is to discuss the role of mesenchymal stem cells (MSCs), which are known to possess regulatory functions on the immune system, as a means of alleviating or eliminating the more severe consequences of the cytokine storm along with pneumonia, two symptoms most commonly associated with death in infected patients.

2. COVID-19-induced pneumonia

Pneumonia refers to the filling of air vesicles in the lung with an inflammatory fluid. Viruses, bacteria and rarely even fungal infections cause pneumonia as a complication of infection. These pathogens begin to attack cells that form the lining of the lungs and inflame small sacs where gaseous exchange occurs. The breathing of a patient becomes shorter and harder, and as the cells die, the lungs become filled with fluids and debris further reducing breathing capacity, and secondary infections can develop as a result. This condition is called pneumonia. In severe cases, the patient requires a respirator to assist their breathing, although the ventilator may not prove effective in some individuals, and this is dependent on the specific reaction of a patient's immune system. That is, the response mounted by the immune system will dictate a patient's outcome. The immune system of critically ill patients becomes overly activated, a condition called cytokine storm, where a large number of white blood cells are activated and release inflammatory cytokines that further activate more white blood cells (18,19).

Pneumonia appears to be the most common severe manifestation of COVID-19, distinguished primarily by fever, dry cough, dyspnoea and bilateral infiltrates on chest imaging (18). Models to predict outcomes of patients infected with COVID-19 take into account three factors: i) The severity of the infection, host response, physiological reserve and comorbidities; ii) the ventilatory responsiveness of the patient to hypoxemia and the time elapsed between the onset of the disease; and iii) the unique observations/manifestations in patients and the capacity of individual hospitals to manage patients. The balance between these factors leads to the development of a time-related disease spectrum with two primary phenotypes. Type L is characterized by low elastance, low ventilation-to-perfusion ratio, low lung weight and a low capacity to recruit immune system actors. Type H is characterized by high elastance, high right-to-left shunt, high lung weight and high a high capacity to recruit immune system actors (19-22).

3. Cytokine storm

Cytokine storm syndrome refers to a range conditions which ultimately manifests as systemic inflammation, multi-organ failure, hyperferritinemia and, if untreated, often death (23). Numerous pathogenic viruses and bacteria have been found to induce cytokine storms or hypercytokinemia (24-26). These pathogens disrupt the balance between a physiological and pathophysiological inflammatory response, pushing from being beneficial to destructive via positive feedback in immune cells and upregulation of proinflammatory markers, in particular cytokines such as TNF-α, IL-1β, IL-8 and IL-6. This results in symptoms such as hypotension, fever and oedema, and may eventually result in organ dysfunction and death (27).

Pathogen-induced lung injury can progress to acute lung injury or its more severe form, acute respiratory distress syndrome (ARDS), as observed with patients infected with SARS-CoV or influenza viruses (28). A hallmark of SARS-CoV-2 pathogenesis is the presence of a cytokine storm in the lungs (29). One of the primary mechanisms underlying development of ARDS is the cytokine storm, a deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α and TGF-β, amongst others) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9 and CXCL10, amongst others) by immune effector cells in response to SARS-CoV infection (14,30-32). The cytokine storm initiates a violent attack by the immune system on the host body, resulting in ARDS and multiple organ failure and ultimately death in severe cases of SARS-CoV-2 infection, similar to that observed in patients who were infected with SARS-CoV and MERS-CoV (33). IL-1β is a key cytokine driving proinflammatory activity in bronchoalveolar lavage fluid of patients with lung injury (28). Pathophysiological levels of inflammation in the lungs also can have other systemic effects on other organs (34).

4. MSCs

The self-renewal and differential capacity of stem cells as potential tools for regeneration, restoration or replacement therapies in a variety of disease conditions has been described previously (35). MSCs are a heterogeneous population of cells with the potential to differentiate into a range of somatic lineages, and were originally described as adherent cells with a fibroblast-like appearance capable of differentiating into osteocytes, chondrocytes, adipocytes, tenocytes and myocytes (36-38). MSCs also support haematopoiesis, possess immunomodulatory properties and specifically migrate to damaged sites. MSC migration is mediated by growth factors, chemokines, adhesion molecules and toll-like receptors (39). MSCs have been successfully used to reverse graft-versus-host disease in patients receiving bone marrow transplants (40,41), particularly in patients diagnosed with severe steroid resistance (42-44). Similarly, in patients with systemic lupus erythematosus and Crohn's disease, both autologous and allogeneic MSCs are able to suppress inflammation and reduce damage to the kidneys and bowel, possibly through the induction of regulatory T cells (45-48).

Immunomodulatory role of MSCs. Following COVID-19 infection-mediated initiation of immune overreaction in the body, the immune system produces large quantities of inflammatory factors, causing a cytokine storm, including an overproduction of immune cells and cytokines (49). At present, there are no specific antiviral treatments recommended for treatment of COVID-19, and no vaccines are currently widely available. Antibacterial agents are ineffective due to the viral nature of the infection. Thus, therapeutic strategies are limited to palliative care and assisted ventilation for patients with severe pneumonia (50).

MSCs are considered a promising tool for cell therapy, in particular for management of inflammatory diseases, based

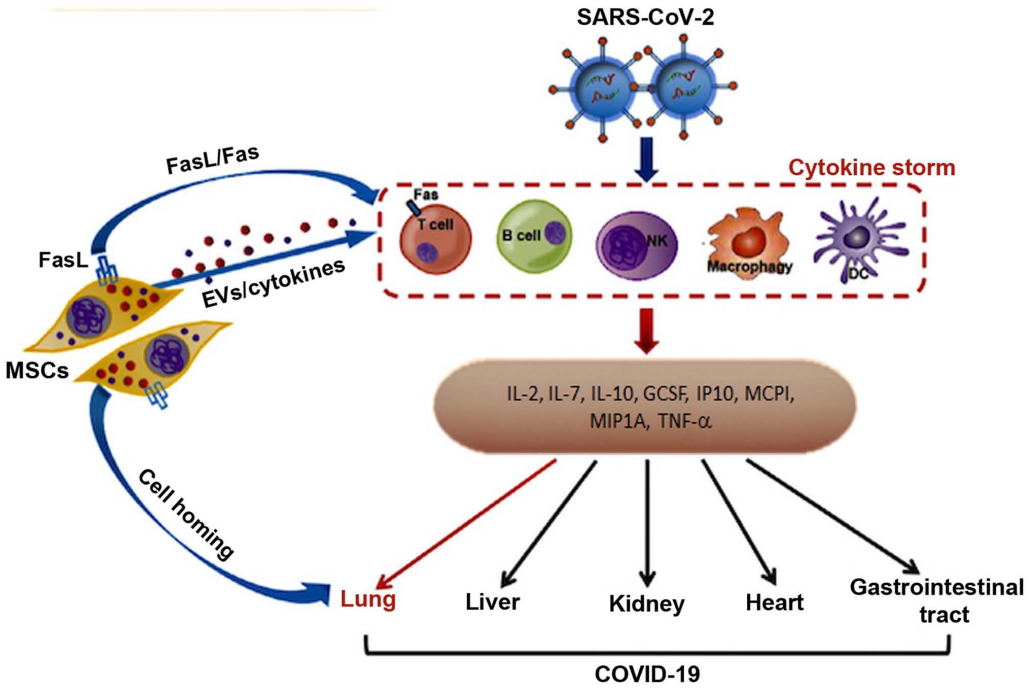

Figure 1. Potential mechanism by which MSCs may manage the severe symptoms of COVID-19 (71). MSC, mesenchymal stem cell; EV, extracellular vesicles; NK, natural killer; DC, dendritic cell.

on their immunomodulatory properties and paracrine effects through trophic factors with anti-fibrotic, anti-apoptotic or pro-angiogenic properties (51,52). MSCs regulate the function of a broad range of immune cells (52-59) and are activated by inflammatory mediators released from activated immune cells (such as IFN-γ, IL-1β and TNF-α) (60,61).

Studies have suggested that MSCs may exhibit immunosuppressive or immunomodulatory properties (53,61,62-65). MSCs are hypothesized to possess the ability to reduce inflammatory effects and defend against a cytokine storm (66). MSCs home in on the injured site due to the presence of local cytokine storm, produced by secretion of activated immune cells. Activation and migration of MSCs results in secretion of multiple immunomodulatory and growth factors. Depending on the cytokine signal (acute vs. chronic inflammation), MSCs initiate the immunoregulatory response and repair the injured site, or are unable to inhibit the persisting chronic inflammatory signals being generated as a result of cellular fibrosis (67).

Alleviation of acute respiratory disease and reversal of pulmonary fibrosis in SARS-CoV-2-infected patients is mediated by three curative properties of MSCs: i) Directly inducing the apoptosis of activated T cells to relieve the aberrant and excessive immune responses; ii) homing toward specific sites of injury in the lung to maintain homeostasis as well as promote regeneration; and iii) releasing cytokines to diminish the inflammatory response and release of extracellular vesicles to stimulate tissue repair (Fig. 1) (68). Notably, it has been shown that cytokines released by MSCs may potently inhibit neutrophil intravasation and enhance the differentiation of macrophages (69,70).

Due to a lack of expression of co-stimulatory molecules and HLA-II, MSCs are regarded as non-immunogenic cells, thus transplantation into an allogeneic host may not require the use of immunosuppressive treatments (71,72). Moreover, MSCs possess immunomodulatory properties and can suppress and inhibit the activation, maturation and proliferation of innate and adaptive immune cells (B cells, T cells, NK cells, dendritic cells and macrophages) (73).

Following intravenous injection of MSCs (systemic infusion), a proportion of the injected cells are trapped in the lung, and this is normally considered a limitation of currently used administration methods. However, with regard to treatment of COVID-19 infection, this may prove beneficial, as these trapped MSCs may promote repair of the pulmonary microenvironment, protect alveolar epithelial cell regeneration, intercept pulmonary fibrosis and reduce lung dysfunction resulting from the COVID-19 infection and pneumonia (13).

Umbilical cord cells, umbilical cord blood, Wharton's jelly, menstrual blood, dental pulp and commercially produced-MSCs are important sources of MSCs that should be assessed in clinical trials as potential treatment of patients infected with COVID-19. However, the process of developing novel therapeutic strategies and introducing them in a clinical setting may result in identification of important practical implications/complications which may not have taken into consideration beforehand (74).

5. Conclusions

Due to the novel coronavirus, >27 million individuals have been infected and almost 900,000 deaths COVID-19-realted deaths have been reported (correct as of 8th of September, 2020). Whilst certain patients infected with COVID-19 do not shown symptoms, predominantly younger healthy individuals, a range of symptoms have been reported, which vary from those with mild complaints (mild fever, cough and, transient loss of taste or smell, amongst others) to more severe symptoms which require admittance to intensive

care and assisted mechanical ventilation. The absence of a definitive treatment for management of the disease and the absence of a vaccine imposes limitations on the management of the spread of the disease, and thus has required governmental bodies to rely on more rudimentary measures, such as social distancing and lockdowns of certain regions to reduce the spread. In addition, the unique immune systems of patients react differently, and the extent of the cytokine storm produced by an individuals may result in death if excessive. It is hypothesized that the use of mesenchymal stem cells for their immunomodulatory properties may result in improved patient outcomes. As mesenchymal stem cells are pluripotent stromal stem cells, they may be successful in treatment and management of COVID-19 infection due to their immune regulatory properties, and thus may be useful for treating patients who develop more severe symptoms. However, additional studies, including clinical trials and meta-analyses are required before widescale adoption in a clinical setting.

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IC and MT both wrote and revised the article. Both authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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