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Mini Review

Role of Mesenchymal Stem Cell Therapy to Treat Pulmonary Fibrosis Caused by SARS-COV-2

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Abstract

Initially, SARS-CoV-2 caused viral pneumonia; however, subsequent experience has shown that it manifests throughout the body, resulting in pathologies of the immune, renal, cardiac, and nervous systems. However, accumulating studies have reported its deleterious effects on lungs. With the better understanding of the chronic and subacute consequences of COVID-19, it is necessary to focus research efforts on finding therapies to reduce acute damage in a targeted manner while restoring physiological function and addressing the long-term consequences of this disease. Recent studies have demonstrated that mesenchymal stem cells may help to restore the lung microenvironment by preserving the alveolar epithelial cells and preventing the lung fibrosis which gives the hope that mesenchymal stem cells therapy could be the main strategy for reducing the recent pandemic. Hence, here we attempted to provide a brief overview of previously reported research work on stem cell therapy for the treatment of pulmonary fibrosis caused by SARS-COV-19.

Introduction

COVID-19 is an acute respiratory infectious disease caused by SARS-COV 2 (Severe Acute Respiratory Syndrome Coronavirus) that has become a global pandemic [1]. It has been A global pandemic has been triggered by a severe respiratory infection caused by a severe respiratory syndrome virus (SARS-COV-2) and named as Coronavirus Disease 2019 (COVID-19) [2]. COVID-19 is characterized by fever, cough, and irritation of the respiratory tract; some patients develop acute and chronic lung injuries, such as Acute Respiratory Distress Syndrome (ARDS) and Pulmonary Fibrosis (PF). Approximately 300 thousand people have died and the number is still increasing; the only way to prevent the spread of the disease is to remain safe until vaccines and treatments become available. COVID-19 is mainly responsible for respiratory complications from Acute Respiratory Distress Syndrome (ARDS), cytokine storms, and severe immune disruptions [1].

A devastating effect in SARS-CoV-2-infected patients is a severe acute respiratory syndrome, the symptoms including fever, cough, fatigue, shortness of breath, and loss of smell [2]. With the progress of the disease, acute lung injury might lead to ARDS or PF. Histopathological findings have shown the occurrence of interstitial fibrosis in a critical patient with COVID-19 [3] in addition to ARDS. Further analysis reveals that the cytokine storm syndrome is profoundly different between deceased and discharged COVID-19 patients [4].

Recent studies have demonstrated that mesenchymal stem cells may help to restore the lung microenvironment, preserve alveolar epithelial cells, prevent lung fibrosis, and treat pulmonary dysfunction caused by COVID-19-associated pneumonia by suppressing aggressive inflammatory reactions and increasing endogenous restoration. Furthermore, clinical evidence has suggested that intravenous injections of mesenchymal stem cells could significantly reduce lung tissue damage in COVID-19 patients. Moreover, with the advancement of research involving mesenchymal stem cells for COVID-19, mesenchymal stem cells therapy could be the main strategy for reducing the recent pandemic. Hence, this review aimed to lay the groundwork for future research by summarizing the previously reported research work on stem cell therapy for the treatment of pulmonary fibrosis caused by SARS-COV-19.

Pathophysiology Through which SARs-COV 2 Cause Pulmonary Fibrosis

Although PF may be seen in other respiratory viral diseases as well, it is more common after SARS-CoV infection [2]. However, the mechanisms of SARS-CoV infection-related PF remain to be fully understood. Activation of Transforming Growth Factor b (TGFb) pathway and increased degradation of Angiotensin-Converting Enzyme2 (ACE2) or angiotensinogen system-mediated lung fibrosis may play major roles [2].

COVID-19 mainly affects the respiratory system resulting in pulmonary fibrosis, based on clinical, radiographic, and autopsy reports. Though patients survive the acute phase of the disease and are even discharged, a major proportion of the affected individuals die from pulmonary fibrosis [1]. In the inflammatory phase of ARDS, there is dysregulation of matrix metalloproteinase, which can cause epithelial and endothelial

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damage, resulting in uncontrolled fibrosis [5]. The continuous activation of epithelial cells may contribute to cellular senescence and overproduction of chemokines, vascular inhibitors, pro-fibrotic growth factors, and coagulation factors. These kinds of factors are collectively called Senescence Associated Secretory Phenotype factors (SASP) [1]. In fibrotic lungs, the fibroblasts and myofibroblasts are the markers of stress and senescence, causing resistance to apoptosis and excessive production of Extra Cellular Matrix components (ECM) [1].

Although PF may be seen in other respiratory viral diseases as well, it is more common after SARS-CoV infection. However, the mechanisms of SARS-CoV infection-related. Moreover, PF is more common after SARS-CoV infection than other respiratory viral diseases. However, the mechanisms of SARS-CoV infection-related PF remain to be fully understood [2]. In addition to activating the Transforming Growth Factor (TGF) pathway and increasing degradation of the Angiotensin-Converting Enzyme 2 (ACE2), the angiotensinogen system may play an important role in lung fibrosis [2]. During the early phase of SARS infection, elevated levels of TGFb1 have been reported [6]. Besides, TGFb pathway activation leads to fibrin, collagen, and matrix metalloproteinases (MMPs). According to further studies, TGFb induces lung fibroblasts to differentiate into myofibroblasts after lung injury, which is crucial for pulmonary tissue repair [2].

Among the explanations for aggravated severe illness in COVID-19 patients is the excessive immune response associated with Cytokine Release Syndrome (CRS), which contributes to lung tissue damage, repair imbalance, and respiratory failure [7]. Eventually, the patient may die from multiple organ failure [8]. Chronic inflammatory syndrome, or CRS, is an aberrant systemic inflammatory response triggered by numerous factors including severe infections and certain drugs. Clinically, the condition is characterized by the rapid appearance of a large number of cytokines within a short period of time. According to an analysis of plasma cytokine levels in 41 confirmed cases of COVID-19 in China, levels of IP-10, MCP-1, MIP-1A, MIP-1B, PDGF, TNF-α, and VEGF were significantly higher in ICU and non-ICU patients [9]. High concentrations of IL-6, GCSF, CRP, and TNF-α have been found in COVID-19 patients [10].

ARDS is associated with hyperproliferation of matrix metalloproteinases, leading to epithelial and endothelial damage, and ultimately uncontrolled fibrosis [11]. These factors are collectively called senescence-associated secretory phenotypes (SASP) [12]. SASP factors can lead to abnormal wound healing, characterized by abnormal crosstalk between epithelial and mesenchymal cells, and the subsequent accumulation of myofibroblasts [6]. It has been observed that fibroblasts and myofibroblasts in fibrotic lungs show signs of stress and senescence, including resistance to apoptosis and excessive production of extracellular matrix components [13]. Moreover, fibrosis could result from this increase in matrix stiffness, which leads to irreversible tissue damage [14].

Collectively stating that fibrosis of the lungs is a chronic, progressive, fibrotic interstitial disease with a poor prognosis [15]. Currently, it has no effective treatment. Based on previous coronavirus infections, such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), as well as current clinical evidence from Coronavirus disease 2019, SARS-CoV-2 infection is likely to cause PF, which has a negative impact on patient prognosis and quality of life [15]. Hence, PF prevention and treatment can not only aid in improving the overall well-being of patient's outcomes after SARS-COV-2 but also reduce overall social and economic burdens.

Role of MSCs in Ameliorating the Effects of Covid

To date, only supportive care has proven to be beneficial for patients with SARS, including mechanical ventilation or in-line suction [2]. Despite being frequently used by patients, ribavirin is ineffective, and the risk of hemolysis is approximately 76% [16]. The use of steroids may prevent the cytokine storm, but retrospective studies have shown bone damage to occur [17]. Despite all rational treatment measures, physicians have failed to achieve the expected results in the COVID-19 pandemic, including drugs against autoimmune and human immunodeficiency viruses (such as hydroxychloroquine) [17].

Multiple clinical trials have demonstrated the safety of MSCs as a therapeutic agent for a variety of diseases. Due to their immunomodulatory and antifibrotic properties, MSCs can be useful in combating SARS CoV-2[1]. Moreover, MSCs also secrete other paracrine soluble factors, such as HGF, EGF, ANGPT1, and IL-10. As a result of these factors, the epithelial and endothelial repair is enhanced and inflammation is reduced. While paracrine signaling has been found to inhibit the TGF-β induced SMAD2 phosphorylation by HGF [1].

A number of preclinical studies have shown that MSCs are hypoimmunogenic for alloreactive T-cells and can promote hematological healing [18]. For instanc, a study by Khoury et al. showed systemic MSC administration could potentially reduce lung injury after respiratory tract infections such as influenza [19]. Additionally, cell therapy is an option for direct or indirect effects, such as improved regeneration and antiinflammation [2].

There are, however, a number of safeties, scalability, consistency, and regulatory concerns that prevent millions of SARS-CoV-2 patients from receiving MSC transplantation [20]. Nonetheless, exosomes or Extracellular Vesicles (EVs) derived from MSCs present another potential option for the large numbers of COVID-19 patients, since MSCs cultured in vitro can continuously shed large amounts of exosomes into the conditioned media instead of dying shortly after transplantation in vivo. Exosomes reduce inflammation, promote edema clearance, restore leaky epithelial membranes, and reduce other sequelae of cytokine storms [21-22]. Exosomes from MSCs have shown therapeutic effects in animal models of acute lung injury (ALI), ARDS, fibrosis, and other inflammatory diseases [7].

Trials testing MSCs to treat acute lung injury, pulmonary fibrosis, and severe and critically ill COVID-19 are underway. In order to support clinical research and MSC transformation, it is necessary to observe the efficacy of MSCs in the treatment of SARS-COV-2 induced pulmonary fibrosis and analyze the possible mechanism, in addition to clinical trials of current MSCs for Idiopathic Pulmonary Fibrosis (IPF) and COVID-19 [15].

Considering the above promising results from preclinical studies and clinical trials, MSCs may prove to be an effective treatment for BLM-induced PF, including IPF and viral-induced PF. Further studies are needed to determine whether MSCs can reverse established pulmonary fibrosis and improve pulmonary function

Conclusion and Future Perspective

Collectively, MSCs have been suggested to ameliorate cytokine release syndrome (CRS) and protect alveolar epithelial cells by secreting many kinds of factors, demonstrating safety and possible efficacy in COVID-19 patients with acute respiratory distress syndrome (ARDS). Thus, suggesting that out of all the therapies touted for COVID-19 treatment, mesenchymal stem cells (MSCs) or MSC-like derivatives have been the most promising so far. However, more work needs to be done. Although several clinical trials have shown the safety and efficacy of intravenous MSCs in patients with COVID-19-related lung diseases, the unclear heterogeneity of the sources of MSCs and thus their secretory and immunomodulatory capabilities make it difficult to compare and learn from the results of different clinical trials. A future focus should be on the development, dissemination, and international agreement of clinical standards to quantify the quality, consistency, and efficacy of stem cell therapies, proper completion, and publication of existing clinical trials, and the development of scalable technologies and resources to produce the large numbers of stem cells needed in a public health crisis. Since nobody knows when the current COVID-19 crisis will end, or when the next crisis will occur

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