

MINI REVIEW

Current Stem Cell Research Status on Hepatic and Pulmonary Sclerosis in COVID-19

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ABSTRACT

Since 2019, Coronavirus Disease (COVID-19) has changed the concept of systemic sclerosis caused by viral infectious diseases. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative organism of COVID-19, has infected more than 1.36 billion people in 188 countries, and nearly 2.29 million have died. Although we have rapidly developed vaccines against COVID-19, the struggle to treat COVID-19 patients who exhibit complicated multiple organ sclerosis has continued ever since. Studies have reported that preexisting liver disease in 3-8% of patients increases metabolic dysfunction and mortality by 4-6-fold in association with the severity of COVID-19. Moreover, both confirmed and cured COVID-19 patients have been reported to develop pulmonary fibrosis, which is often related to poor prognosis of the complications. Therefore, in the present study, we summarize the possible mechanisms underlying the development of hepatic and pulmonary fibrosis caused by SARS-CoV-2 infection, based on recently published data. Furthermore, since stem cell-based treatments have been developed as a novel approach to treat COVID-19 patients with Systemic Sclerosis (SS), we discuss the implementation of stem cell-based treatments as a powerful regenerative tool owing to their notable immunomodulatory and anti-fibrotic effects.

INTRODUCTION

The most severe manifestations of coronavirus disease are atypical pneumonia and sepsis; however, the gastrointestinal tract and liver have recently been reported to be highly affected by SARS-CoV-2. SS generally develops due to fibrosis, which is a pathological process that involves the excessive accumulation of extracellular matrix components, such as collagen, fibronectin, and hyaluronic acid. If this phenomenon persists for a prolonged period, it can lead to a rare chronic autoimmune disease with extensive microvascular injury, endothelial cell damage, activation of immune responses, and progression of tissue fibrosis in various internal organs, especially the liver and lungs.

Various mechanisms underlying the development of hepatic and pulmonary sclerosis in COVID-19 patients have been described, including viral and immune-mediated mechanisms [1]. SARS-CoV-2 is a single-stranded, positive-sense RNA virus belonging to the family Coronaviridae [2]. The sequence homology of SARS-CoV-2 with SARS-CoV and MERS-CoV is 79.5% and 50%, respectively [3]. SARS-CoV-2 binds to the human cells via Angiotensin-Converting Enzyme 2 (ACE2), which is expressed in the liver and lungs [4-6]. Interestingly, ACE2, which serves as the host cell receptor of SARS-CoV-2, plays a protective role against liver and lung damage and is expressed in hepatocytes [7-10].

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To date, various therapeutic methods have been employed to manage the symptoms of SS. Studies conducted over several decades have led to the identification of many potential targets to combat fibrotic tissue damage; however, no effective therapies or U.S. Food and Drug Administration (USFDA)-approved antifibrotic agents are currently available [11]. Therefore, the development of antifibrotic therapies to date has relied mainly on a comprehensive understanding of profibrogenic mechanisms in multiple organ systems as well as disease-specific locations [11].

Stem cell-based treatments have been developed as a novel approach to treat several autoimmune diseases. Stem cells, specifically Mesenchymal Stem Cells (MSCs), can be applied as a powerful regenerative tool. They can be advantageous for SS treatment due to their notable immunomodulatory and anti-fibrotic effects. Accordingly, here, we discuss the contemporary status and future perspectives of MSC transplantation for SS treatment [12]. In this review, we reported the current status and highlighted all the implications associated with stem cell therapy for COVID-19.

COVID-19 and hepatic sclerosis

Prior to the emergence of COVID-19 pandemic, cirrhosis and hepatocellular carcinoma accounted for more than 2.5% of all deaths worldwide [13]. Liver cirrhosis leads to immune dysfunction characterized by immunodeficiency and systemic inflammation, which makes patients highly susceptible to SARS-CoV-2 infection. The reported incidence of liver injury associated with COVID-19 ranges from 14.8-53% [14]. Studies reported that SARS-CoV-2 directly binds to ACE2 expressed hepatocytes and cholangiocytes. Importantly, the expression level of ACE2 is much higher in cholangiocytes than hepatocytes (59.7% vs. 2.6%) [15]. Furthermore, SARS-CoV-2 infection impaired the bile acid transportation from cholangiocytes via altering gene involved in canaliculi formed by tight junction [16]. It could lead to liver injury because cholangiocytes has important roles in hepatic regeneration and immune response. A previous study reported that 1 out of 99 COVID-19 patients exhibited a pathological lesion with severe hepatocellular damage and elevated ALT and AST levels, whereas the rest of the patients exhibited moderately elevated ALT and AST levels [17]. The main physiological changes reported to date

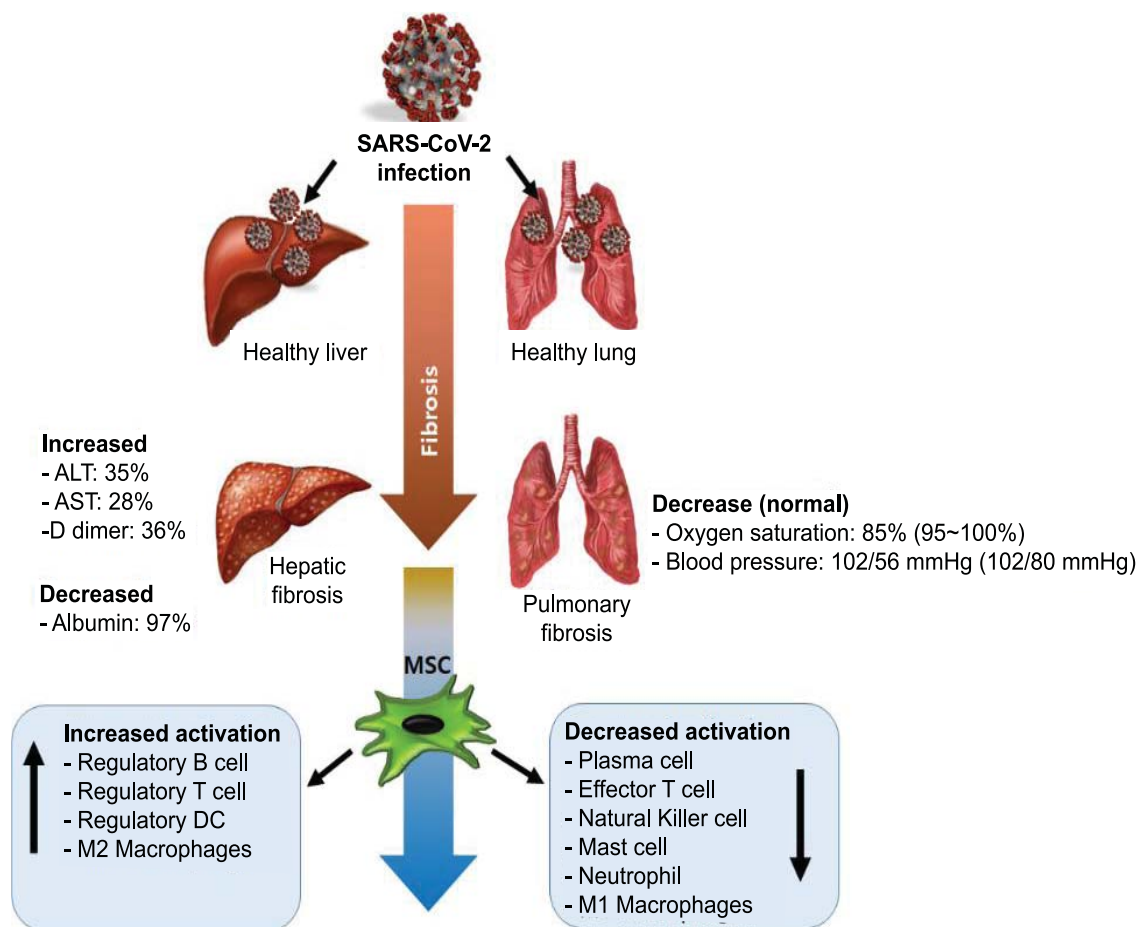


Figure 1 Summary of physiological and cytochemical changes in the progression of hepatic and pulmonary fibrosis in COVID-19 patients and the potential for improved immune response by MSC therapy.

include increased alanine Aminotransferase (ALT, 13.3–35%), Aspartate aminotransferase (AST, 28–37%), Gamma-Glutamyl Transferase (GGT, 54%), and total bilirubin levels [18]. On the other hand, serum albumin levels was significantly decreased as low as 97% [17]. Furthermore, liver compromise has been associated with the most severe cases of COVID-19.

COVID-19 and pulmonary sclerosis

Pulmonary sclerosis, also known as pulmonary fibrosis, is a condition wherein chronically damaged lung tissue becomes fibrotic and scarred over time. Major symptoms of pulmonary sclerosis include shortness of breath, dry cough, tiredness, weight loss, and nail clubbing. The most common complications associated with pulmonary sclerosis include pulmonary hypertension, respiratory failure, pneumothorax, and lung cancer. Studies have also shown (i) direct evidence of hepatic and pulmonary fibrosis by performing autopsy and pulmonary puncture pathology and (ii) indirect evidence of increased levels of fibrosis-related cytokines [e.g., Transforming Growth Factor (TGF- β), Tumor Necrosis Factor- α (TNF- α), interleukin-6, and interleukin-10] in the peripheral blood of severe patients. To develop a potential treatment against SS, the three major fibrosis-related signaling pathways—TGF- β , Wingless and int (WNT), and YAP/TAZ (known as essential regulators of cell adhesion and cell-cell communication)—in pulmonary fibrosis should be targeted using drugs or stem cell therapy [19,20]. Furthermore, the therapeutic potential of pirfenidone and nintedanib for treating idiopathic as well as COVID-19-induced pulmonary fibrosis should be examined.

Stem cell therapy for sclerosis

Currently, the drugs used to treat COVID-19, such as remdesivir (anti-viral drug), tocilizumab (a drug for rheumatoid arthritis), statins (a drug for cardiovascular disease as HMG-CoA reductase inhibitors), azithromycin (antibiotic for bacterial pneumonia), and chloroquine (a drug for malaria and several inflammatory diseases), exhibit marked hepatotoxic potential, and the patients administered these drugs may develop drug-induced liver injury. Therefore, stem cell therapy may be considered as an alternate treatment option that is currently available for SS associated with COVID-19. MSCs and MSC-like cells exert robust immunomodulatory, regenerative, and anti-fibrotic effects on myofibroblast-mediated fibrotic disease. The recent use of stem cell therapy for critically ill COVID-19 patients in a small group of patients in China as well as the subsequent emergency use authorization of stem cell therapy by the USFDA to the Global Institute of Stem Cell Therapy and Research and Athersys have garnered interest in the medical community for its clinical applications. Consequently, several clinical trials on stem cell-based COVID-19 treatment, which aim to use different cell

sources, doses, and diverse targeted patient groups, have been registered [21]. MSC-based therapy for COVID-19 has been suggested to ameliorate cytokine release syndrome and protect alveolar epithelial cells by secreting different types of factors, demonstrating safety and possible efficacy in COVID-19 patients with acute respiratory distress syndrome [22].

Most registered clinical trials have proposed to use MSCs because of their immunomodulatory effects. However, using MSCs to treat immunocompromised COVID-19 patients raises a concern regarding the greater risk of viral and other infections in these patients. Since the immunosuppressive effect of MSCs is non-specific, both alloantigen and viral antigen responses could be repressed, thereby leading to detrimental clinical outcomes. Therefore, recent studies have suggested that exosomes might play an important role in fibrotic diseases and have focused on exosomal cargo dysregulation and their potential diagnostic and therapeutic values in fibrosis [23]. Interestingly, in a recent study, genetically modified hepatocyte growth factor-secreting MSCs effectively decreased the severity of hepatic sclerosis in a corresponding rat model [24]. However, few studies have also reported an association between hepatic sclerosis and COVID-19.

CONCLUSION

In addition to the shortage of donors for organ transplantation, hepatic and pulmonary sclerosis patients now face a new challenge in the form of COVID-19, which can be life threatening. A major challenge encountered by the scientific community and funding agencies is to develop a successful, highly effective, and sophisticated treatment for major organ sclerosis associated with SARS-CoV-2 infection using stem cell therapy. Since a limited number of clinically approved cell therapies are being pursued as the promising options, there is an urgent need to find more effective candidate therapies while testing the current candidates for sclerosis. In addition to the identification of novel drug treatments and validation of their therapeutic potential, we need to identify novel sclerosis targets as well as cell sources for soft organ sclerosis, which would strengthen our arsenal in the fight against organ sclerosis associated with COVID-19. Understanding stem cell biology in further detail will also broaden our strategies for its control and clinical application worldwide.

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