

World Journal of *Gastroenterology*

World J Gastroenterol 2021 May 7; 27(17): 1847-2053



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The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Report® cites the 2019 impact factor (IF) for WJG as 3.665; IF without journal self cites: 3.534; 5-year IF: 4.048; Ranking: 35 among 88 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2019 is 7.1 and Scopus CiteScore rank 2019: Gastroenterology is 17/137.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yan-Jie Ma*; Production Department Director: *Xiang Li*; Editorial Office Director: *Ze-Mao Gong*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

May 7, 2021

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<https://www.wjgnet.com/bpg/GerInfo/287>

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<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

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<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Mesenchymal stromal cell secretome in liver failure: Perspectives on COVID-19 infection treatment

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Author contributions: Chinnici CM, Russelli G, Bulati M, Miceli V, Gallo A, Busà R, Tinnirello R, Conaldi PG and Iannolo G conducted the research and edited all drafts of the manuscript.

Supported by UPMC International, Pittsburg, United States, No. I0000026; Italian Ministry of Education, University and Research, Rome, Italy, No. CTN01_00177_888744; and PO FESR Sicilia 2014/2020 Azione 1.1.5 Project (Prometeo), No. 08PA8610200270.

Conflict-of-interest statement: The authors declare having no conflicts of interest.

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Abstract

Due to their immunomodulatory potential and release of trophic factors that promote healing, mesenchymal stromal cells (MSCs) are considered important players in tissue homeostasis and regeneration. MSCs have been widely used in clinical trials to treat multiple conditions associated with inflammation and tissue damage. Recent evidence suggests that most of the MSC therapeutic effects are derived from their secretome, including the extracellular vesicles, representing a promising approach in regenerative medicine application to treat organ failure as a result of inflammation/fibrosis. The recent outbreak of respiratory syndrome coronavirus, caused by the newly identified agent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has forced scientists worldwide to use all available instruments to fight the infection, including the inflammatory cascade caused by this pandemic disease. The use of MSCs is a valid approach to combat organ inflammation in different compartments. In addition to the lungs, which are considered the main inflammatory target for this virus, other organs are compromised by the infection. In particular, the liver is involved in the inflammatory response to SARS-CoV-2 infection, which causes organ failure, leading to death in coronavirus disease 2019 (COVID-19) patients. We herein summarize the current implications derived from the use of MSCs and their soluble derivatives in COVID-19 treatment, and emphasize the potential of MSC-based therapy in this clinical setting.

Key Words: Mesenchymal stromal cell; COVID-19; SARS-CoV-2; Organ failure;

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Manuscript source: Invited
manuscript

Specialty type: Gastroenterology
and hepatology

Country/Territory of origin: Italy

**Peer-review report's scientific
quality classification**

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 27, 2021

Peer-review started: January 27,
2021

First decision: February 24, 2021

Revised: March 5, 2021

Accepted: April 5, 2021

Article in press: April 5, 2021

Published online: May 7, 2021

P-Reviewer: Li Q, Suzuki YJ

S-Editor: Gao CC

L-Editor: Filipodia

P-Editor: Liu JH



Inflammation; Transplantation

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Core Tip: The recent coronavirus disease 2019 (COVID-19) pandemic outbreak has forced scientists worldwide to use all available options to fight this disease, in particular the inflammatory cascade caused by this infection. Mesenchymal stromal cells, for their immunomodulatory potential, represent a valid approach to combat organ inflammation. The main targets for this virus are the lungs, while other organs such as the liver are compromised by the infection. Evaluation of the albumin role in COVID-19 patients, and the connection to the “capillary leak syndrome” have focused attention on liver dysfunction correlated with the infection.

Citation: Chinnici CM, Russelli G, Bulati M, Miceli V, Gallo A, Busà R, Tinnirello R, Conaldi PG, Iannolo G. Mesenchymal stromal cell secretome in liver failure: Perspectives on COVID-19 infection treatment. *World J Gastroenterol* 2021; 27(17): 1905-1919

URL: <https://www.wjgnet.com/1007-9327/full/v27/i17/1905.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v27.i17.1905>

INTRODUCTION

The liver can be damaged by various factors, including cytotoxic molecules, ischemia, metabolic alterations, or viral infections[1], which result in inflammatory responses contributing to further liver damage[2]. If the inflammation persists, a transition from acute to chronic injury can occur, inducing hepatic fibrosis[2]. Therefore, therapies that can reduce liver inflammation/fibrosis are crucial in order to avoid organ failure and the need for transplantation.

In recent years, the use of mesenchymal stromal cells (MSCs) has been considered a promising therapeutic approach to treat liver injuries[3]. MSCs can be isolated from different compartments including adipose tissue[4], umbilical cord[5], bone marrow[6], or placenta[7,8]. These cells have been successfully used in different therapeutic applications aimed at reducing inflammatory responses[9]. Moreover, the infusion of MSCs immediately after liver transplantation promotes organ regeneration and prolonged recipient survival by reducing acute inflammation[10].

Despite their beneficial properties, there are several limitations to the use of MSCs for cellular therapies; for example, their plasticity causes the potential risk of differentiation into undesired tissues and the possibility of malignant transformation is under debate[11,12]. To overcome these issues, the use of cell-free therapy is gaining considerable attention as a treatment for liver injury, an alternative to conventional cell transplantation[13]. Indeed, the regenerative properties of the MSC secretome include immunomodulatory effects mediated by growth factors and cytokines, such as transforming growth factor beta (TGF-β), prostaglandin E2, indoleamine 2,3-dioxygenase, hepatocyte growth factor (HGF), interleukin-10 (IL-10), and tumor necrosis factor alpha (TNF-α)[14,15], which can also attenuate fibrogenesis. In addition, the MSC therapeutic effects could also result from the released extracellular vesicles (EVs). EVs include a highly heterogeneous group of vesicles of different size able to modulate the immune responses[16,17]. Indeed, MSC-derived EVs can be selectively enriched with anti-fibrotic[18] and anti-apoptotic[19] factors, as well as specific non-coding RNA with therapeutic potential[20].

In December 2019, several cases of death from pneumonia were reported in Wuhan, later related to a new coronavirus-related disease called coronavirus disease 2019 (COVID-19). Analysis of its genome revealed it to be phylogenetically related to severe acute respiratory syndrome coronavirus (SARS-CoV)[21], and for this reason it was named SARS-CoV-2 by the World Health Organization (WHO). Due to its worldwide spread, the WHO declared COVID-19 a pandemic in March 2020. Angiotensin-converting enzyme 2 receptor (ACE2), highly expressed in the respiratory tract, was considered the main SARS-CoV-2 viral attachment for animal cells. Most likely for this reason, the lungs are the principal target organs for SARS-CoV-2[22,23]. This virus triggers an exacerbated immune reaction because large amounts of different

inflammatory factors, including cytokines and chemokines, are produced by immune reactive cells.

It has been hypothesized that MSC-based therapy for COVID-19 patients can prevent the development of a cytokine storm by activating the immune system and promoting organ repair[24,25]. Intravenously injected MSCs reach the lungs, where they engraft and secrete a variety of soluble factors including anti-inflammatory factors, angiogenic factors, and EVs[26,27]. Studies aimed toward reversing COVID-19 side effects through MSC treatment are ongoing. In this review, we summarize the therapeutic potentials of the MSC secretome for treating liver injuries associated with COVID-19.

MSC SECRETOME AND EVS FOR ORGAN INJURY

The use of MSC-based therapy for regenerative medicine applications counts in the hundreds of registered clinical trials (www.clinicaltrial.gov) because of the ability of these cells to promote immunomodulation and organ regeneration[28]. The release of trophic factors has demonstrated that their action is in part attributable to their secretome and, in particular, to secreted EVs[29]. Because of their intrinsic therapeutic potential, EVs are a powerful tool of regenerative medicine for the treatment of a wide range of diseases[30]. Due to heterogeneity in size and contents, as well as lack of specific markers, distinguishing the various EV subtypes is an ongoing challenge. According to the International Society for Extracellular Vesicles (ISEV), the generic term EVs includes nano-sized particles naturally released into the extracellular space by all cell types; they are delimited by a lipid bilayer and cannot replicate[31]. The ISEV consensus suggests considering physical parameters (*e.g.*, size or density) to distinguish “small” EVs, often referred as “exosomes” (< 100-200 nm in diameter) from “medium/large” EVs or “microvesicles” (> 200 nm). EVs are replete with diverse proteins, lipids, carbohydrates, and nucleic acids, and exert many of their functions of intercellular communicators by transferring their cargo molecules among cells. The specific cargo composition of EVs is largely defined by the tissue/cell type from which they originate[32]. Similarly to EVs from other cell types, MSC-EVs can be characterized according to the guidelines indicated by the ISEV. The available data suggest that EVs may significantly contribute to the paracrine effects of MSCs on tissue regeneration[33]. Because of EVs’ broad biological functions, as well as their ability to transfer molecules between cells, MSC-EV-based therapy represents an attractive alternative to cell-based therapy. Application of MSC-EVs as a cell-free therapy has several advantages over conventional cell therapy. Primarily, EV injection carries lower safety risks because of their minimal reactivity to the immune system, and seem to be generally well tolerated, even when used xenogenically[34]. Then, because of their small size compared to MSCs, the intravenous delivery of EVs presents lower risk of vascular obstructions. Finally, EVs can also be genetically manipulated to carry desired therapeutic cargo for a broad, expanding range of potential clinical applications. The number of studies demonstrating the therapeutic potential of MSC-EVs in different disease models is growing rapidly. The beneficial effects of MSC-EV-based treatment are evidenced especially in cardioprotection and angiogenesis[35].

Understanding the mechanisms of action behind the therapeutic effects of MSC-EVs are crucial in view of their future clinical applications. Despite increasing interest, this field is still in its infancy in identifying the relevant bioactive molecules released by MSC-EVs that play a role in tissue repair. Efforts to identify these molecules lead to the conclusion that MSC-EVs preferentially contain mRNAs and microRNAs (miRNAs) targeting genes that participate in several cellular pathways involved in tissue repair, such as angiogenesis, migration, proliferation, self-renewal, differentiation, cellular transport, and apoptosis[36,37]. The overexpression of certain miRNAs can contribute to enhancing the therapeutic efficacy of MSC-EVs. For example, MSC-EVs overexpressing miR-21 have neuroprotective effects by targeting several genes involved in the inhibition of cell apoptosis[38,39]. The list of miRNAs known to increase the therapeutic potential of MSC-EVs in numerous disease models is long, and their therapeutic effects range from tumor modulation, immune suppression, and angiogenesis to tissue regeneration[40].

In addition to miRNAs, the beneficial effect of EV-derived proteins has been explored in terms of tissue repair and anti-inflammatory effects as a treatment for liver fibrosis, ischemia, myocardial infarction, acute renal injury, neural regeneration, or in the context of bone and cartilage regeneration[40]. Proteins identified in MSC-EVs and

linked to tissue repair include glial-derived neurotrophic factor, vascular endothelial growth factor, fibroblast growth factor, HGF, and angiotensin 1[41].

Although the number of clinical studies is limited, growing evidence shows the beneficial effects of MSC-EVs on tissue injuries. The impact of MSC-EVs on tissue regeneration has been investigated in several animal models of neuronal, cardiac, bone, cartilage, kidney, muscle, wound healing, respiratory injury, and liver regeneration[41,42]. Interestingly, data from animal models indicate that MSC-EVs can exert therapeutic potential similar to their cellular origin[41,43-46]. The list of registered clinical trials (<https://clinicaltrials.gov>) reporting tissue injuries-treated with MSC-EVs is shown in Table 1.

MSC-EVs show great potential as a regenerative medicine treatment for liver diseases. The benefits of MSC-EVs in liver diseases are documented in animal models of both acute[20] and chronic[47] liver injuries. MSC-EVs exert a beneficial effect by alleviating fibrosis and improving regeneration of hepatocytes[46]. In particular, EVs from fetal MSCs promote hepatocyte proliferation and decrease hepatocyte apoptosis in liver injury induced by carbon tetrachloride[48], or ameliorate oxidative stress in ischemia reperfusion injury (IRI) models in rats[49] and mice[50]. Similarly, EVs of MSC-derived induced pluripotent stem cells have hepatoprotective effects on a rat model of IRI by inducing hepatocyte proliferation[51,52]. Finally, the anti-fibrotic effects of hydrogel-embedded MSC-EVs are documented in chronic liver failure[53]. The results from *in vivo* studies indicate EVs as essential contributors to MSC therapeutic efficacy, and suggest that MSC-EV-based therapy may be a successful alternative to cell-based treatments. Nevertheless, there are still many important questions to be answered before MSC-EVs can become a fully realized cell-free therapy. These challenges comprise studies establishing the exact contribution of EVs to MSC-based therapy, including the underlying molecule mechanisms, or identifying which EV population is the most therapeutically effective. In addition, a major ongoing debate in the field of MSC EV-based therapy concerns the purity of the obtained vesicles due to contamination of the samples with non-EV proteins, RNAs, and lipoproteins[41].

LIVER FAILURE IN COVID-19 PATIENTS

SARS-CoV-2 is the etiological agent of the pandemic COVID-19, characterized by respiratory distress and/or hypoxemia, fever, fatigue, dry cough and, in severe cases, septic shock, metabolic acidosis, and death[54]. SARS-CoV-2, as with other corona viruses, enters the host cells by binding to the ACE-2 receptor[55], while the serine protease transmembrane serine protease 2 is required for S protein priming[56]. Despite the higher tropism for the respiratory tract, SARS-CoV-2 also targets other tissues, given that the ACE2 receptor is widely distributed in other tissues[57-61]. To shed light on the SARS-CoV-2 tropism, Nardo *et al*[62] analyzed, on the Human Protein Atlas, the expression levels of two proteins, ACE-2 receptor and TMPRSS2, in different human tissues, thus revealing a higher expression in the intestine and gall bladder, but their absence in the liver. A single-cell analysis, performed on healthy human liver samples, showed that while ACE-2 expression level in cholangiocytes is comparable to that of alveolar cells in the lungs, it is barely detectable in hepatocytes[63]. Interestingly, the liver cell line HuH7 is an established permissive cell type for both SARS-CoV and SARS-CoV-2 infection, and has recently been extensively used as a model in SARS-CoV-2 studies[64,65]. In addition, an *in vitro* study found that SARS-CoV-2 infection leads to a decrease of cholangiocellular tight junction protein claudin 1 mRNA expression, implying a reduced barrier function of cholangiocytes[66]. The presence of SARS-CoV-2 receptors in the gastrointestinal (GI) tract suggests an important role of the hepatobiliary tract in viral replication and excretion[67]. In fact, the virus has also been isolated from stool samples[68]. The involvement of the GI tract in COVID-19 disease is confirmed by the GI symptoms occurring in more than 60% of infected patients, as lack of appetite, loss of smell and taste, anorexia, diarrhea, abdominal pain, nausea, and vomiting[69-74]. Moreover, post-mortem biopsies of SARS-CoV-2-infected patients showed the presence of the viral genome in hepatocytes and the GI tract by reverse transcription polymerase chain reaction (RT-PCR)[75-77].

Though liver failure in COVID-19 patients has been considered marginal, the incidence of hepatic tissue injury in these patients ranges from 14.8% to 53%[78], while mortality ranges from 58.06% to 78%[79,80]. The liver is a key organ in nearly all metabolic processes, has immunologic functions, and is the main detoxifying organ.

Table 1 List of registered clinical trials on the use of mesenchymal stromal cell-derived extracellular vesicles for tissue injury

Tissue injury disease	Condition	Treatment	Trial ID	Status
Chronic lung disease	Pediatric bronchopulmonary dysplasia	BM-MSC-derived EVs	NCT03857841	Phase I
Lung disease	Pneumonia, COVID-19	BM-MSC-derived EVs	NCT04493242	Not yet recruiting
Lung disease	Pneumonia, COVID-19	Inhalation of mesenchymal stem cell exosomes	NCT04276987	Phase I
Multiple organ failure	Multiple organ dysfunction syndrome	MSC exosomes	NCT04356300	Not yet recruiting
Lung disease	Pulmonary infection	MSC exosomes	NCT04544215	Recruiting
Dry eye	GVHD	UC-MSC exosomes	NCT04213248	Recruiting
Cartilage injury	Osteoarthritis	Secretome or EVs from adipose MSCs	NCT04223622	Not yet recruiting
Skin disease	Dystrophic epidermolysis bullosa	BM-MSC EVs	NCT04173650	Phase II
Brain	Cerebrovascular disorders	Allogenic MSCs enriched with miR-124	NCT03384433	Phase II

BM: Bone marrow; COVID-19: Coronavirus disease 2019; EV: Extracellular vesicle; GVHD: Graft-*vs*-host disease; MSC: Mesenchymal stromal cell; UC: Umbilical cord.

Moreover, because of the production of albumin, acute phase reactants and coagulation factors, the liver can strongly affect the multisystem manifestations of COVID-19[62]. In fact, modified levels of hepatic function indicators such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, gamma-glutamyl transferase, and bilirubin have been observed in patients with COVID-19, and principally in severe diseases[59,81-84]. Many studies have shown that liver injury occurs in the early stage of the disease, with mild or moderate increase of ALT, AST, or bilirubin together with a decrease in albumin levels[79,85,86]. High AST levels have been associated with the highest mortality risk[57,87], while decreased albumin levels have been associated with severe infection and poor prognosis[88,89]. Since the specific pathogenetic mechanism by which the virus causes liver injury is still unclear, many hypotheses have been offered, including immune-mediated damage. The triggering of an exacerbated immune response to the viral infection leads to a massive release of cytokines and inflammation mediators known as cytokine storm, which is responsible for immune-mediated liver damage[89] (Figure 1).

High levels of cytokines and chemokines (*i.e.* IL-1 β , IL-2, IL-6, IL-8, IL-10, IL-17, interferons [IFNs], IFN-induced protein 10, TNF- α , granulocyte-macrophage colony-stimulating factor [GM-CSF], monocyte chemoattractant protein-1, macrophage inflammatory protein-1 α) and other inflammatory molecules (PCR, ferritin, lactate dehydrogenase, D-dimer) have been observed in severe SARS-CoV-2-infected patients[54,57,88,90-92]. This highly inflammatory milieu leads to multiorgan damage, including liver failure, and is strictly linked to poor prognosis and death in COVID-19 patients[88,90]. As confirmation, liver samples from COVID-19 patient autopsies have revealed micro-vesicular steatosis and inflammation[93-95]. In fact, SARS-CoV-2 infects both hepatic cells and bile duct epithelium, causing liver impairment by direct cytopathic effect, as demonstrated by high transaminase levels and post-mortem liver biopsy specimens showing moderate micro-vesicular steatosis and mild lobular and portal activity[79]. Furthermore, the presence of SARS-CoV-2 has been found in parenchymal cells and vascular endothelium of the liver in COVID-19 patients[76,77].

Additional causes of liver injury can include hypoxia, hypovolemia, and microvascular thrombosis. The hypoxic state associated with COVID-19 can induce ischemic/hypoxic liver injury[87-89]. Considering that COVID-19 patients suffer from severe hypoxia, with the induction of ACE2 receptor expression on hepatocytes[96], a direct infection of hepatocytes by SARS-CoV-2 in hypoxic conditions has been suggested[25]. Liver injury can also be drug-induced. Most of the drugs used against SARS-CoV-2 are potentially hepatotoxic: Antivirals (lopinavir/ritonavir, remdesivir, umifenovir), antibiotics (macrolides, quinolones), chloroquine, tocilizumab, and steroids as well as antipyretic drugs used for fever in COVID-19[79,90,97,98]. Moreover, it must be considered that the majority of COVID-19 patients developing liver complications have a pre-existing chronic liver disease, rendering them more susceptible to liver injury. Interestingly, it has been reported that liver fibrotic/cirrhotic conditions lead to an increase of ACE-2 receptor expression in hepatocytes[96], thus suggesting again a possible role of pre-existing pathological liver

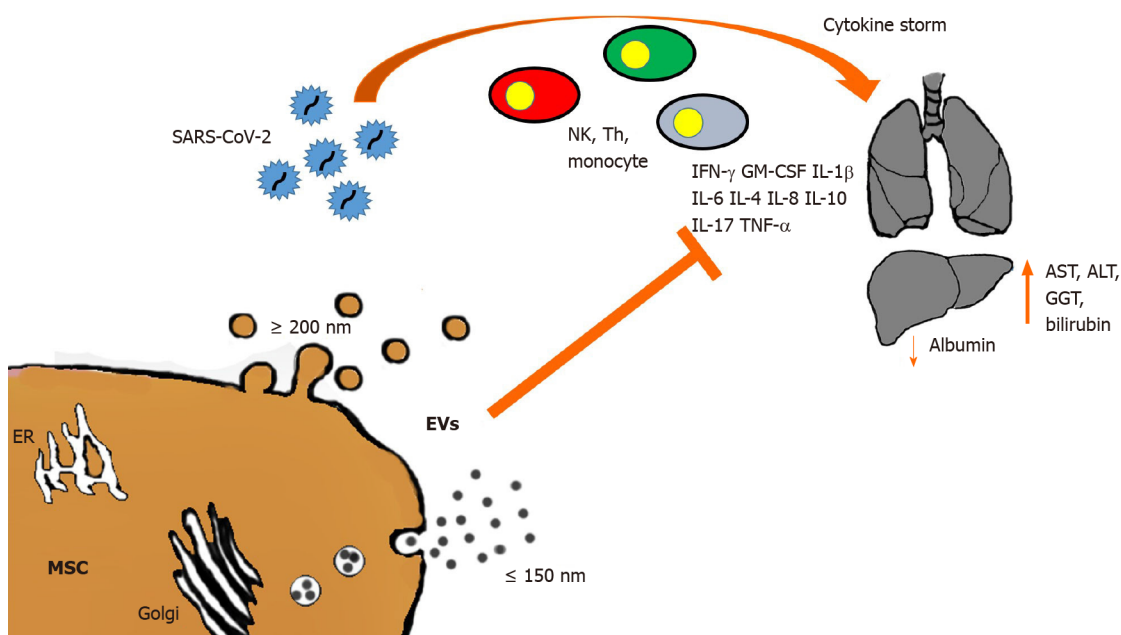


Figure 1 Schematic representation of severe acute respiratory syndrome coronavirus 2 impact on lungs and liver. Cytokine storm with the cascade triggered by natural killer (NK) cells, T helper (Th) cell and monocytes, and the production of inflammatory cytokines (interleukin 1 beta [IL-1 β], IL-2, IL-6, IL-8, IL-10, IL-17, interferons [IFNs], IFN-induced protein 10, tumor necrosis factor alpha, granulocyte-macrophage colony-stimulating factor [GM-CSF]). The infection in the liver causes an increase in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) and bilirubin, and a decrease in albumin. Mesenchymal stromal cells (MSCs) can reduce the inflammatory response by extracellular vesicle (EV) release (large ≥ 200 nm and small ≤ 150 nm). ER: Endoplasmic reticulum; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

conditions in exacerbating SARS-CoV-2 hepatic tropism.

MSCS AND IMMUNOMODULATION IN COVID-19

The immunomodulatory properties of MSCs represent a promising therapeutic approach for the treatment of autoimmune and inflammatory diseases[99]. The anti-inflammatory and regenerative properties of MSCs have been established in numerous preclinical models of immune-related disorders including graft-*vs*-host disease, sepsis, inflammatory bowel disease, and allergic airway disease[100-103]. Recent phase I/II clinical trials have shown that the infusion of MSCs immediately after liver transplantation promoted organ regeneration and prolonged recipient survival by reducing acute inflammation, thus suggesting that MSCs can be a promising candidate for cell-based immunotherapy in solid organ transplantation[10,104]. In addition, murine models of liver fibrosis showed that human MSC-derived EVs are able to reduce hepatic inflammation and fibrosis through a decrease of TGF- β , IFN- γ , IL-1, IL-2 and TNF- α levels, an increase of Treg numbers, and a reduction of collagen deposition, all acting together to combat necrosis in the liver[105-107] (Figure 1). Among others, liver injury has been reported as a common complication in SARS-CoV-2 infection, with the degree of liver damage strictly related to the severity of COVID-19[92,108-110]. Although the exact mechanism of liver injury in COVID-19 patients is still unknown, it has been suggested that either the progression of pre-existing hepatic diseases or a direct damage of the liver can be associated with the systemic inflammation caused by SARS-CoV-2 infection, toxicity of anti-viral drugs, or hypoxia-reperfusion injury[109,110].

Pathogenic T cells are rapidly activated after SARS-CoV-2 infection, thus producing GM-CSF, IL-6, and other proinflammatory factors. GM-CSF will further activate inflammatory monocytes (CD14⁺CD16⁺), which in turn produce a larger amount of IL-6 and other pro-inflammatory factors, triggering the cytokine storm, which is the main cause of the organ damage, such as in the lungs, kidney, and liver[110]. Recently, the use of MSCs has been proposed as a promising therapeutic approach for COVID-19 patients. The effectiveness and safety of MSC-based treatment are supported by several clinical studies, suggesting that MSC therapy may improve the clinical outcomes of COVID-19 patients through immunomodulation, regulation of

inflammatory response, and promotion of tissue repair[111-115]. Moreover, a vast number of clinical trials that use MSCs to treat COVID-19 have already been registered (<http://www.chictr.org.cn>; <https://clinicaltrials.gov>). According to their immunomodulatory properties, the use of MSC-based therapies could be a novel strategy to counteract the harmful effects on the liver caused by SARS-CoV-2 infection.

DISCUSSION

Among the numerous drug treatments, which include antiviral therapy, cytokine inhibitors (*e.g.*, IL-6), and specific antibody treatment (serum/monoclonal)[116], MSCs represent a potential option for critical cases[117]. As discussed above, SARS-CoV-2 infection induces a cytokine storm, causing acute respiratory distress syndrome and multiple-organ failure. IL-6 inhibition by tocilizumab was positively tested in a randomized clinical trial (<http://www.chictr.org.cn/showproj.aspx?proj=49409>). Likewise, in this inhibition MSCs can represent a valid alternative, and it has been shown that EV administration counteracts IL-6-induced acute liver injury (ALI) in rat models through the presence of miR-455-3p[118]. MSC treatment showed that the symptomatology of patients was relieved within 2-4 d after MSC infusion, with oxygen saturation increasing to 95% at rest[119]. Another study involved critically ill COVID-19 patients treated with an infusion of human umbilical cord MSCs. In this case, the patients were treated with three different infusions of cells at an interval of 3 d, displayed no observable side effects, and were able to walk within 4 d[115]. Leng *et al*[119] showed that after infusion of MSCs in COVID-19 patients, the number of peripheral lymphocytes increased, while the levels of C-reactive protein decreased. In addition, in MSC-treated COVID-19 patients compared with those treated with conventional therapy a clear reduction of the major pro-inflammatory cytokine TNF- α , and an increase of IL-10 concentration were observed[119]. Therefore, in an immune-mediated disease condition like COVID-19 infection, the anti-inflammatory activities of MSCs could contribute to improving the conditions of patients after their infusion.

Despite the limited published data, and based on various studies, it could be speculated that SARS-CoV-2 induces ALI[79]. SARS-CoV-2 could insult the liver either directly, by the cytopathic effect of the virus after infections of the hepatocytes, or indirectly, by induction of uncontrolled immune reaction, oxidative stress, and/or by pharmacological treatments for COVID-19 that induce liver injury. However, the mechanisms underlying liver impairment in COVID-19 patients are still unknown. Tian *et al*[94] found sinusoidal dilatation and focal macrovesicular steatosis in liver biopsies obtained post-mortem from four patients with COVID-19 and, in one of these, SARS-CoV-2 RNA was isolated from liver tissue. Wang *et al*[73] found that four patients (2.9% of 138 patients hospitalized for COVID-19) had chronic liver disease. In another study, cases of ALI were reported in 13 of 274 patients (4.7%)[120]. Interestingly, Richardson *et al*[121] showed that, in a study including 5700 COVID-19 patients, 58.4% and 39% developed higher levels of ALT and AST, respectively. In addition, among these patients, 56 (1%) developed acute hepatic injury (32320003). Therefore, many COVID-19 patients showed higher levels of both ALT and AST, and mainly in patients with severe disease, liver impairment can occur[54,59,120].

The intravenous administration of MSCs lowered the elevated serum levels of AST and ALT, and increased the amount of HGF, resulting in reduction of ALI[122]. Moreover, in a rat model of ALI, MSCs inhibited neutrophil infiltration, oxidative stress, and hepatocyte apoptosis[123], showing that MSC treatment had significant systemic anti-inflammatory effects and reduction of hepatic inflammation. Moreover, MSCs can prevent lung damage not only directly, with anti-inflammatory activity, but also indirectly by supporting liver function in maintaining the plasma level of albumin (Figure 1). Johnson *et al*[124] recently underscored the interplay between albumin and SARS-CoV-2, while the importance of albumin in COVID-19 patients has also been strongly stressed by several research teams, who describe a “capillary leak syndrome” in infected patients. This extravascular leakage of intravascular fluids is induced by hypoglobulinemia[125]. A histological analysis of COVID-19 lungs in SARS-CoV-2-infected patients confirmed the presence of pulmonary vascular permeability where the endothelial cells appear swollen[126]. Hypoalbuminemia is an indication of liver dysfunction in the elderly, where it is, *per se*, an index of increased mortality[127]. The large amounts of extravascular fluid due to the resulting vascular permeability, require mechanical ventilation to overcome the problem.

CONCLUSION

At present, there is no standardized therapy for COVID-19 patients. Though many innovative treatments have been rapidly approved, additional experimental therapies are necessary to treat the worse cases of infection. Despite the fact that all MSC clinical trials for COVID-19 treatment are currently focused on lung/respiratory function, and some of the exclusion criteria are liver disease/insufficiency, we believe, on the basis of current studies, that MSC-based therapy can also help liver dysfunction correlated with SARS-CoV-2 infection.

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