

World Journal of *Stem Cells*

World J Stem Cells 2021 August 26; 13(8): 971-1159



REVIEW

- 971** Differences and similarities between mesenchymal stem cell and endothelial progenitor cell immunoregulatory properties against T cells
Razazian M, Khosravi M, Bahiraii S, Uzan G, Shamdani S, Naserian S
- 985** Inter-regulatory role of microRNAs in interaction between viruses and stem cells
Afshari A, Yaghobi R, Rezaei G
- 1005** Mesenchymal stem cells for enhancing biological healing after meniscal injuries
Rhim HC, Jeon OH, Han SB, Bae JH, Suh DW, Jang KM
- 1030** Modulating poststroke inflammatory mechanisms: Novel aspects of mesenchymal stem cells, extracellular vesicles and microglia
Xin WQ, Wei W, Pan YL, Cui BL, Yang XY, Bähr M, Doeppner TR

MINIREVIEWS

- 1049** Antler stem cells and their potential in wound healing and bone regeneration
Zhang W, Ke CH, Guo HH, Xiao L
- 1058** Therapeutic prospects of mesenchymal stem/stromal cells in COVID-19 associated pulmonary diseases: From bench to bedside
Zhang LS, Yu Y, Yu H, Han ZC
- 1072** Mesenchymal stem cells as a potential therapeutic tool to cure cognitive impairment caused by neuroinflammation
Skok M
- 1084** Effects of radiation and chemotherapy on adipose stem cells: Implications for use in fat grafting in cancer patients
Platoff R, Villalobos MA, Hagaman AR, Liu Y, Matthews M, DiSanto ME, Carpenter JP, Zhang P
- 1094** Methods to produce induced pluripotent stem cell-derived mesenchymal stem cells: Mesenchymal stem cells from induced pluripotent stem cells
Dupuis V, Oltra E
- 1112** Central nervous system tumors and three-dimensional cell biology: Current and future perspectives in modeling
Abou-Mrad Z, Bou Gharios J, Moubarak MM, Chalhoub A, Moussalem C, Bahmad HF, Abou-Kheir W
- 1127** Regulators of liver cancer stem cells
Liu K, Ou JHJ

SYSTEMATIC REVIEWS

- 1134** Induced pluripotent stem cells as suitable sensors for fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome

Monzón-Nomdedeu MB, Morten KJ, Oltra E

CASE REPORT

- 1151** Treatment of acute ischemic stroke by minimally manipulated umbilical cord-derived mesenchymal stem cells transplantation: A case report

Ahn H, Lee SY, Jung WJ, Lee KH

ABOUT COVER

Editorial Board Member of *World Journal of Stem Cells*, Radwa A Mehanna, MD, PhD, Professor, Physiology Department, Vice Executive Manager, Center of Excellence For Research in Regenerative Medicine and its Applications CERRMA, Faculty of Medicine, Alexandria University, Alexandria 21561, Egypt.
radwa.mehanna@alexmed.edu.eg

AIMS AND SCOPE

The primary aim of *World Journal of Stem Cells (WJSC, World J Stem Cells)* is to provide scholars and readers from various fields of stem cells with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJSC* publishes articles reporting research results obtained in the field of stem cell biology and regenerative medicine, related to the wide range of stem cells including embryonic stem cells, germline stem cells, tissue-specific stem cells, adult stem cells, mesenchymal stromal cells, induced pluripotent stem cells, embryonal carcinoma stem cells, hemangioblasts, lymphoid progenitor cells, etc.

INDEXING/ABSTRACTING

The *WJSC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Biological Abstracts, BIOSIS Previews, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJSC* as 5.326; IF without journal self cites: 5.035; 5-year IF: 4.956; Journal Citation Indicator: 0.55; Ranking: 14 among 29 journals in cell and tissue engineering; Quartile category: Q2; Ranking: 72 among 195 journals in cell biology; and Quartile category: Q2. The *WJSC*'s CiteScore for 2020 is 3.1 and Scopus CiteScore rank 2020: Histology is 31/60; Genetics is 205/325; Genetics (clinical) is 64/87; Molecular Biology is 285/382; Cell Biology is 208/279.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Xia Xing; Production Department Director: Yu-Jie Ma; Editorial Office Director: Ze-Mao Gong.

NAME OF JOURNAL

World Journal of Stem Cells

ISSN

ISSN 1948-0210 (online)

LAUNCH DATE

December 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Shengwen Calvin Li, Tong Cao, Carlo Ventura

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-0210/editorialboard.htm>

PUBLICATION DATE

August 26, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

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

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

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

PUBLICATION ETHICS

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

PUBLICATION MISCONDUCT

<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>



Therapeutic prospects of mesenchymal stem/stromal cells in COVID-19 associated pulmonary diseases: From bench to bedside

Lei-Sheng Zhang, Yi Yu, Hao Yu, Zhong-Chao Han

ORCID number: Lei-Sheng Zhang 0000-0001-6540-0943; Yi Yu 0000-0002-1911-3692; Hao Yu 0000-0002-8355-8741; Zhong-Chao Han 0000-0002-1365-1844.

Author contributions: Zhang LS and Yu Y contributed equally to this work; Zhang LS and Yu Y performed data analysis and interpretation, and manuscript writing and revision; Zhang LS, Yu H, and Han ZC conceptualized and designed the study, and approved the final manuscript; all the coauthors have read and approved the publication of the manuscript.

Supported by Shandong Provincial Natural Science Foundation, No. ZR2020QC097; China Postdoctoral Science Foundation, No. 2019M661033; Jiangxi Key New Product Incubation Program Funded by Technical Innovation Guidance Program of Shangrao city, No. 2020G002; Tianjin Science and Technology Project for Overseas Students, No. JH-20180070802; Natural Science Foundation of Tianjin, No. 19JCQNJC12500; Major Project of Fundamental Research Funds of the Central Public Welfare Scientific Research Institutes of the Chinese Academy of Medical Sciences, No. 2018PT31048; Major Project of Fundamental Research Funds of the Central Public

Lei-Sheng Zhang, Qianfoshan Hospital & The First Affiliated Hospital, Shandong First Medical University, Jinan 250014, Shandong Province, China

Lei-Sheng Zhang, Yi Yu, Zhong-Chao Han, State Key Laboratory of Experimental Hematology & National Clinical Research Center for Blood Disease, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin 300020, China

Lei-Sheng Zhang, Hao Yu, School of Medicine, Nankai University, Tianjin 300071, China

Lei-Sheng Zhang, Zhong-Chao Han, Precision Medicine Division, Health-Biotech (Tianjin) Stem Cell Research Institute Co., Ltd., Tianjin 301700, China

Yi Yu, The First Affiliated Hospital, Zhejiang University, Hangzhou 310003, Zhejiang Province, China

Hao Yu, Zhong-Chao Han, Cell Products of National Engineering Center & National Stem Cell Engineering Research Center, Tianjin IMCELL Stem Cell and Gene Technology Co., Ltd., Tianjin 300457, China

Corresponding author: Hao Yu, PhD, Associate Professor, School of Medicine, Nankai University, No. 94 Weijian Road, Nankai District, Tianjin 300071, China.
yuhao-wuhan@hotmail.com

Abstract

The ongoing outbreak of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 has become a sudden public emergency of international concern and seriously threatens millions of people's life health. Two current studies have indicated a favorable role for mesenchymal stem/stromal cells (MSCs) in clinical remission of COVID-19 associated pulmonary diseases, yet the systematical elaboration of the therapeutics and underlying mechanism is far from satisfaction. In the present review, we summarize the therapeutic potential of MSCs in COVID-19 associated pulmonary diseases such as pneumonia induced acute lung injury, acute respiratory distress syndrome, and pulmonary fibrosis. Furthermore, we review the underlying mechanism of MSCs including direct- and trans-differentiation, autocrine and paracrine anti-inflammatory effects, homing, and neovascularization, as well as constitutive microenvironment. Finally, we discuss the prospects and supervision of MSC-based cytototherapy for COVID-19 management

Welfare Scientific Research Institutes of the Chinese Academy of Medical Sciences, No. 2019PT310013; National Science and Technology Major Projects of China for "Major New Drugs Innovation and Development", No. 2014ZX09508002-003; National Natural Science Foundation of China, No. 81330015; and Science and Technology Project of Tianjin, No. 17ZXSCSY00030.

Conflict-of-interest statement: The authors have no conflicts of interest to disclose.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Cell and tissue engineering

Country/Territory of origin: China

Peer-review report's scientific quality classification

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

Received: February 8, 2021

Peer-review started: February 8, 2021

First decision: March 8, 2021

Revised: March 10, 2021

Accepted: April 20, 2021

Article in press: April 20, 2021

Published online: August 26, 2021

P-Reviewer: Tanabe S

S-Editor: Fan JR

before large-scale application in clinical practice. Collectively, this review supplies overwhelming new references for understanding the landscapes of MSCs in the remission of COVID-19 associated pulmonary diseases.

Key Words: Mesenchymal stem/stromal cells; COVID-19; Acute lung injury; Acute respiratory distress syndrome; Pulmonary fibrosis; Molecular mechanism

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Coronavirus disease 2019 (COVID-19) is a global pandemic and seriously threatens people's lives. Due to the limitation of current traditional remedies as well as the rapid disease progression, patients with severe pulmonary manifestations and accompanied comorbidities are inclined to worse outcomes. Herein, we review the latest updates of the mesenchymal stem/stromal cells-based cytotherapy for COVID-19 management, and discuss the principles and underlying molecular mechanisms as well, which will collectively benefit the novel comprehensive treatment for COVID-19 cases.

Citation: Zhang LS, Yu Y, Yu H, Han ZC. Therapeutic prospects of mesenchymal stem/stromal cells in COVID-19 associated pulmonary diseases: From bench to bedside. *World J Stem Cells* 2021; 13(8): 1058-1071

URL: <https://www.wjgnet.com/1948-0210/full/v13/i8/1058.htm>

DOI: <https://dx.doi.org/10.4252/wjsc.v13.i8.1058>

INTRODUCTION

The novel pandemic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), designated as coronavirus disease 2019 (COVID-19), initially reported in Wuhan of China, has promptly spread around worldwide as the third coronavirus outbreak in mankind in the 21st century[1-3]. As of January 31, 2021, more than 2139183 of 99.7 million confirmed cases died from COVID-19 according to the dashboard by the Center for Systems Science and Engineering at Johns Hopkins University (www.arcgis.com/apps/opsdashboard/index.html), and the morbidity and mortality rates are congruously higher in elderly patients than in young patients[4,5]. Of them, the majority were diagnosed with pneumonia accompanied with acute lung injury (ALI), acute respiratory distress syndrome (ARDS), secondary pulmonary fibrosis, and even cytokine storm caused multiple system organ failure, which were confirmed by multifaceted analyses including epidemiological, clinicopathologic, and molecular pathogenetic detections[3,5,6].

Despite the distinguishable molecular phenotype and mild mortality rate compared with the SARS-CoV in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, COVID-19 caused by the SARS-CoV-2 displays similarities in efficient human-to-human transmission and pneumonia-associated ALI/ARDS characteristics[3,4]. However, COVID-19 has a more secluded latency for 3-14 d as well as the proportional asymptomatic carriers. Worse still, besides the virus itself and clinical therapeutics, the misleading of public policies (e.g., work resumption and group immunity) and misunderstanding of civilization as well as overzealous human rights and panicstricken psychological responses in facing with the life-threatening COVID-19 further disturb the precautionary measures and make the situation of prevention and control increasingly grim[4,7,8]. Currently, although comprehensive treatments have demonstrated efficaciously ameliorative outcomes of COVID-19 patients, including antibiotics and antiviral drugs, Chinese medicines, anti-inflammatory corticosteroids, and plasma and supportive therapeutics, the clinical grade targeted anti-SARS-CoV-2 drugs and vaccines are still far from reality[4,9]. Considering the serious side effects and contradictory efficacy of different drugs such as glucocorticoid and hydroxychloroquine, there is an urgency of developing novel therapeutic techniques in dealing with cytokine storm and pulmonary damage, especially the recently reported mesenchymal stem/stromal cell (MSC)-based cytotherapy[10,11].

L-Editor: Wang TQ

P-Editor: Yuan YY



MSCs, also acknowledged as medicinal signaling cells, are a heterogenous multipotential population with splendid hematopoietic-supporting and immunoregulatory properties[12,13]. Since the first isolation in bone marrow (BM) by Friedenstein and colleagues in 1968, MSCs of multiple origins have been identified from adult tissues (*e.g.*, adipose, dental pulp, and pancreatic tissue) and perinatal tissues [umbilical cord (UC), placenta chorionic villi, and amniotic membrane and fluid], or derived from human pluripotent stem cells (hPSCs) [*e.g.*, human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs)][14-20]. For decades, we and other investigators have indicated the therapeutic potentials of MSC-based cytotherapy in regenerative medicine such as graft-versus-host disease (GVHD), aplastic anemia, diabetic disease/complication, and acute myocardial infarction (AMI), as well as chronic obstructive pulmonary disease (COPD) and pneumonia induced ALI/ARDS [10,12,13,21-24]. Generally, MSCs function through direct- and trans-differentiation, autocrine and paracrine anti-inflammatory effects, homing, and neovascularization, as well as constitutive microenvironment, yet the accurate mechanism mediating the aforementioned roles remains to be further elucidated[13,23].

In this review, we summarize the current advances on MSCs in COVID-19 associated pulmonary diseases from the view of fundamental and clinical studies. Substantially, we further describe the modes of action as well as underlying molecular mechanism. Finally, we discuss the advantages and supervision of the current advancements in MSC-based therapeutics towards standardization and clinical application.

THERAPEUTIC POTENTIAL OF MSCS IN COVID-19

Pneumonia induced ALI

ALI is one of the major causes of acute respiratory failure with pulmonary manifestations such as diffuse alveolar damage, and the mortality rate of patients with ALI is approximately 40%[25]. Although the underlying therapeutic mechanisms remain incompletely understood, numerous preclinical studies have indicated that administration of MSCs ameliorated ALI. For instance, by utilizing the influenza virus influenza A (H1N1)-induced mice model, Bouvier *et al*[26] and Fukushi *et al*[27] found that the H1N1 virus mainly caused inflammatory lung injury, and dysfunction of congenital and adaptive immune responses followed by viral cytopathic effect, as well as secondary diffuse lung injury, which was further verified by Khatri *et al*[28] in an influenza virus-induced ALI pig model administered with MSC-derived extracellular vesicle (MSC-EVs)[26-28]. Studies on the underlying mechanism suggested that MSC-EVs with anti-inflammatory and anti-influenza properties could incorporate into the H1N1-infected lung epithelial cells and suppress influenza virus replication, virus-induced apoptosis, and the virus-induced accumulation of proinflammatory cytokines. Interestingly, by conducting pre-incubation with RNase enzyme, Khatri *et al*[28] found that the anti-influenza activity of MSC-EVs was abrogated, which indicated the pivotal role of transferred RNA from MSC-EVs to H1N1-infected lung lesions[26-28]. Thus, MSC-EVs were suffice to mimic the beneficial effects of MSCs and attenuate ALI caused by influenza virus and the newly generated COVID-19 *via* simultaneously restraining virus replication and the inflammatory response. In 2014, using a lipopolysaccharide (LPS)-induced ALI mouse model, we found that the pneumonia-induced ALI and immunodysfunction status of mice were efficaciously attenuated by intrapulmonary delivery of human UC-MSCs[29]. Furthermore, Rojas *et al*[30] took advantage of the BM-MSCs to demonstrate the ameliorative effect and no organ toxicity in an LPS-induced ALI sheep model, which are extremely important for clinical translation purposes[30]. In another study, Hao *et al*[31] compared the administration of MSCs derived from BM and embryonic stem cells (BM-MSCs, hESC-MSCs) in an endotoxin-induced ALI mouse model and found that both types of the aforementioned MSCs were sufficient for significantly reducing the cytokine storm-induced inflammation and injured alveolus. However, even with superiority in immunomodulation, hESC-MSCs seemingly did not show beneficial effects on lung protein permeability and pulmonary edema[31]. Hence, there is a crucial need for a disease-specific potency assay to detect the efficacy of MSC-based therapeutics in ALI.

ARDS

ARDS is acknowledge as a devastating pathogenetic process characterized by diffuse alveolar damage and severe hypoxemia, with a mortality rate of 40%, and there are no effective treatment strategies as well[32,33]. As to COVID-19, most patients have

symptoms such as fatigue, cough, and fever, in whom continued progression to ARDS and even death may occur[6,34]. To date, ARDS is considered the most common etiological factor of respiratory failure and the major cause of morbidity and mortality in critically ill patients[31]. For decades, preliminary clinical and preclinical studies have indicated involvement of virus in severe pneumonia and syndromes, and viral pneumonia induced direct lung injury is the proegumenal cause of ARDS[33,35]. Generally, there are two major ARDS models, including the infectious model and sterile inflammatory model, which are derived by direct administration of *Streptococcus pneumoniae* and intratracheal administration of LPS, respectively[33]. As to MSC-based cytotherapy, Zheng *et al*[36] reported the first clinical trial of ARDS treatment with allogeneic adipose-derived MSCs in 12 adult patients at an intravenous dose of 1×10^6 cells/kg of body weight, but the clinical effect was weak and further optimization would be required to reduce alveolar epithelial injury in ARDS[36]. After that, Wilson *et al*[37] further reported a phase 1 clinical trial in 9 patients with moderate-to-severe ARDS with a single intravenous infusion of allogeneic BM-MSCs and confirmed the primary safety and effectiveness though with several highlighted drawbacks[37,38]. Very recently, the safety and efficacy outcomes of a prospective, double-blind, multicenter, randomized phase 2a safety trial conducted in 60 ventilated patients with moderate to severe ARDS were reported by Matthay *et al*[39]. Compared with those in the placebo group, patients with one intravenous dose of MSC administration manifested more reliable safety and effectiveness such as Acute Physiology and Chronic Health Evaluation III and minute ventilation[39]. Above all, of the state-of-art updates upon cell-based therapies including MSCs, endothelial progenitor cells (EPCs), and hPSCs, MSCs are recognized with the most considerable promise and override precedence for allogeneic therapy in clinical application for ARDS treatment [32].

Pulmonary fibrosis

Pulmonary fibrosis is a chronic, refractory, debilitating, and lethal lung disease with multidimensional characteristics such as myofibroblast activation, disruption of pulmonary function with interstitial fibrosis, extensive extracellular matrix (ECM) deposition, and hypoxemic respiratory failure, as well as a 20% survival within 5 years of diagnosis[40,41]. Etiological analyses of pulmonary fibrosis indicated the involvement of invasive immune cell- and secreted cytokine-induced inflammatory microenvironment after pulmonary injury[42,43]. Over the years, preclinical studies of lung fibrosis have enlightened the feasibility of MSCs in the treatment of idiopathic pulmonary fibrosis (IPF) by accelerating epithelial repair and inhibiting inflammation. In 2014, by conducting a single center, non-randomized, dose escalation phase 1b trial, Chambers and colleagues verified the inspiring feasibility and good short-term safety in patients with moderately severe IPF together with minimal acute adverse effects of intravenous MSC administration[44].

UNDERLYING MOLECULAR MECHANISMS

Direct- and trans-differentiation

For decades, pioneering investigators in the field have highlighted the homeostatic role of autogenous and allogeneic MSCs in repairing and replacing the damaged lung tissues[45]. Initial attempts on the mechanism studies for lung disease treatment with MSC administration mainly focused on the exploration of direct evidence for MSC-derived functional cells during rehabilitation of damaged lung tissues, whereas it subsequently proved to be difficult by most investigators in consideration of the insufficiency of the effective retention rate (< 5%)[46].

On the basis of the unique homing property, MSCs principally migrate to the damaged lung tissues through the bloodstream and exercise the restorative function by an orchestration of modulation, whereas only a tiny fraction of them are capable of differentiating into the pulmonary or bronchial epithelial cells. For instance, by utilizing the bleomycin-induced lung injury and fibrosis models together with the fluorescence *in situ* hybridization, Ortiz *et al*[47] demonstrated the significantly alleviated inflammation and collagen deposition of lung tissues were largely attributed to the homing features of MSCs as well as their trans-differentiation into an epithelium-like morphology in the areas of injured lungs in the recipient murine[47]. Similarly, *in vitro* models such as scratch wound assay and coculture experiments further confirmed the protective effects of MSCs on wound healing and primary small airway epithelial cells by increasing the migration and proliferation of epithelial cells

[48,49]. Furthermore, Akram *et al*[48] and Huh *et al*[50] verified the restorative mechanism of MSC-based cytotераpy on cigarette smoke-induced emphysema and inflammatory cytokine-induced impairment of alveolar type II epithelial cells by regulating the keratinocyte growth factor (KGF)-dependent phosphatidylinositol 3-kinase-Akt-mammalian target of rapamycin signaling cascades[50,51].

Autocrine and paracrine anti-inflammatory effects

Intercellular communications among identical and/or different cell types are usually mediated by autocrine and paracrine mechanisms. EVs secreted by MSCs have been consecutively identified in the culture medium under physiological and pathological circumstances[17,28]. Among them, exosomes containing a genetic cargo of subcellular fractions such as mRNA, tRNA, microRNAs, circular RNAs, competing endogenous RNAs, proteins, and bioactive lipids are extensively explored[52,53]. For example, we recently demonstrated that exosomes derived from immune thrombocytopenia plasma played a critical role in impairing the megakaryocyte and platelet generation through a Bcl-xL/caspase signaling mediated apoptosis pathway[54].

Along with the existing effects of MSCs on endogenous progenitor cells in the lung, current paradigms of MSC application in clinical trials primitively focus on anti-inflammatory paracrine rather than structural repairment[9,55]. Cytokine release syndrome is a major underlying pathophysiological process in ARDS, which can be efficaciously suppressed in patients with critically illness associated disorders according to several prospective clinical studies[10,37,39]. As to ALI/ARDS, the therapeutic efficacy of MSCs in inpatients, including alveolar epithelium and lung endothelium repair, inflammation inhibition, and absorption of lung exudate, is largely attributed to the release of a variety of soluble factors, which is consistent with the preclinical models[39,56]. For instance, KGF[57,58] and angiopoietin-1[59] released by MSCs have been shown to protect the alveolar epithelium and endothelium from injury in terms of protein permeability and loss of alveolar fluid clearance during ALI [56,60]. Similarly, a cohort of soluble factors such as interleukin 10, prostaglandin-E₂, and transforming growth factor β (TGF- β), together with antibiotic proteins (*e.g.*, LL37) and antibacterial factors, congruously perform a constructive role in immunologic homeostasis by simultaneously suppressing inflammatory response and stimulating monocyte/macrophage phagocytosis, respectively[56]. Collectively, by secreting the aforementioned soluble factors and accompanied counterparts of subcellular fractions, MSCs have been hypothesized to potentially act as an alternative option for ameliorating severe COVID-19 associated ALI/ARDS by putatively binding to pulmonary alveolar cells and neutralizing the free virus particles, as well as transferring mitochondria from MSCs to damaged lung epithelial cells[61,62].

Homing and neovascularization

Renewal has also prompted the pivotal characteristics of MSCs during multisystem disorders including pulmonary and bronchial diseases by homing facilitating neovascularization in the damaged sites[56]. Generally, in response to the circulating inflammatory cytokines and chemokines in the bloodstream, MSCs are purposefully recruited to the injured sites and thus initiate the therapeutic effects upon emphysema and pneumonia *via* benefiting the generation of small pulmonary vessels or accelerating the reconstruction of other functional cells[51].

To date, the research literature has indicated the beneficial effects of multiple released cytokines in neovascularization, including vascular endothelial growth factor (VEGF), stromal cell-derived factor (SDF-1), basic fibroblast growth factor (bFGF), and TGF. For instance, MSC-secreted VEGF is involved in the migration of trophoblast cells, microtubule formation, and development of angiogenesis by binding to the corresponding receptor VEGF-R and activating the signaling cascades, which also have an incentive role in recruiting stem cells to the damaged or diseased tissue[63]. Dissimilarly, SDF-1 is highly expressed in pulmonary endothelial and epithelial cells, which is adequate for enhancing stem cell activities as well as recruiting angiogenic precursors to the injury sites instead. In consistence with that finding, with the aid of a model of bronchopulmonary dysplasia, Reiter *et al*[64] found that knockdown of SDF-1 in MSCs largely obliterated the therapeutic benefits of MSCs on pulmonary angiogenesis and stem cell recruitment[64]. In addition, other soluble factors including TGF- β and bFGF are mainly involved in accelerating the accumulation pro-angiogenic extracellular matrix proteins and the secretion of VEGF, respectively[19,65,66].

Constitutive microenvironment

Generally, the homeostasis and regeneration of stem cells and the concomitantly

derived cells are tightly regulated by the resident microenvironment[67]. Besides the aforementioned mode of action, MSCs functioned as the dominant component in the microenvironment for hematogenesis and coordinate contributions to multisystem disease occurrence[13,68]. For decades, we and other investigators in the field have verified the promising curative effects of MSC-based cytotherapy on recurrent and refractory disorder remodeling, such as acquired aplastic anemia[13,66], osteoarthritis [69], AMI[21,70], Crohn's disease with enterocutaneous fistula[71], acute-on-chronic liver failure[72], COPD[22], and COVID-19 associated ALI/ARDS[10].

In the context of pulmonary infections, MSCs are adequate to maintain or replenish the stem cell pool in damaged tissues and reconstruct the microenvironment for the succeeding appropriate functioning. This is attributed to their resistance to cytotoxic substances and degraded signal cascades in response to pulmonary injuries as well as the release of multiple factors such as growth factors, ECM, anti-inflammatory cytokines, extracellular organelles, and vesicles, which collectively provide an instructive and permissive environment together with restrict the pneumonia-induced ALI/ARDS by substituting the abnormally regulatory signals in the niche[67,73]. Meanwhile, accumulated evidence has indicated the therapeutic effects of MSCs *via* recruiting or differentiating into functional cells, and even by accelerating the proliferation, dedifferentiation, and trans-differentiation of committed cells after lung injury.

Currently, emerging evidence has suggested the possibilities of MSC-based intervention iatresia for COVID-19 pneumonia management, and in particular, the shortness of breath and respiratory failure caused by severe ARDS[3,74]. Interestingly, Hough and the colleagues verified that MSCs could transfer endothelial mitochondria to impaired alveolar epithelial cells to increase alveolar adenosine triphosphate concentrations, which in turn reduced the endotoxin-induced alveolar injury and thus the increase in pulmonary fluid clearance[75]. Taken together, the multifaceted unique characteristics of MSCs in the niche have endowed rosy prospects and unlimited potential for COVID-19 associated pulmonary diseases (Figure 1).

STANDARDIZATION AND SUPERVISION

Cell products and standardization

Longitudinal progress in fundamental and clinical studies has indicated the preferable therapeutic potential of MSCs in respiratory disease treatment and remission, especially BM-MSCs and UC-MSCs with the most extensive application in clinical trials and the most robust multiplication capacity, respectively[32,68,71]. Distinguishing from other stem cell counterparts including the aforementioned EPCs and hPSCs with greater barriers for autologous therapy, MSCs hold advanced advantages on respiratory diseases[16,32]. However, there is a skeptical voice on the curative effects and variations in quality in considering the allogeneic cell sources and the probability of genetic variability[70,76]. For example, we and Zhang *et al*[14] recently confirmed the multifaceted alterations in efficacy on acute GVHD and acute liver failure, respectively [14,23].

Therewith, considering the discrepancy and potential uncertainty, there is an urgent need to clarify the safety, effectiveness, and reproducibility of MSC-based cytotherapy by systematically and meticulously dissecting the similarities and differences among various cell products, which is the prerequisite for large-scale clinical application as well[23]. For instance, we have reported the diverse variations of biological and genetic properties in UC-MSCs after continuous *in vitro* passages, which would help figure out the controversial effects on disease management and benefit the clinical practice[23].

Aiming to improve the feasibility of MSC-based application in multisystem diseases including COVID-19 caused pneumonia and comorbidities, concerns upon the standardization and scenario of cell products require to be further addressed. First, the convenience and rationalization of sources for large-scale industrial manufacturing should be carefully selected among perinatal tissues (*e.g.*, UC and placenta)[71], adult tissues (*e.g.*, BM, adipose tissue, and dental pulp)[77], and pluripotent stem cells (*e.g.*, hESCs and hiPSCs)[17]. On the basis of the existing literature, it is of importance to launch the manufacture of large-scale, clinical-grade MSCs by building a public cell bank, which will vastly benefit the large-scale production of standardized cell source for regenerative medicine[78]. Second, the production engineering (*e.g.*, pathogen-free conditions, automated or semi-automated operations, stasis or rotation, passage number, and hypoxia) and accompanied supplements (*e.g.*, albumin, serum, and

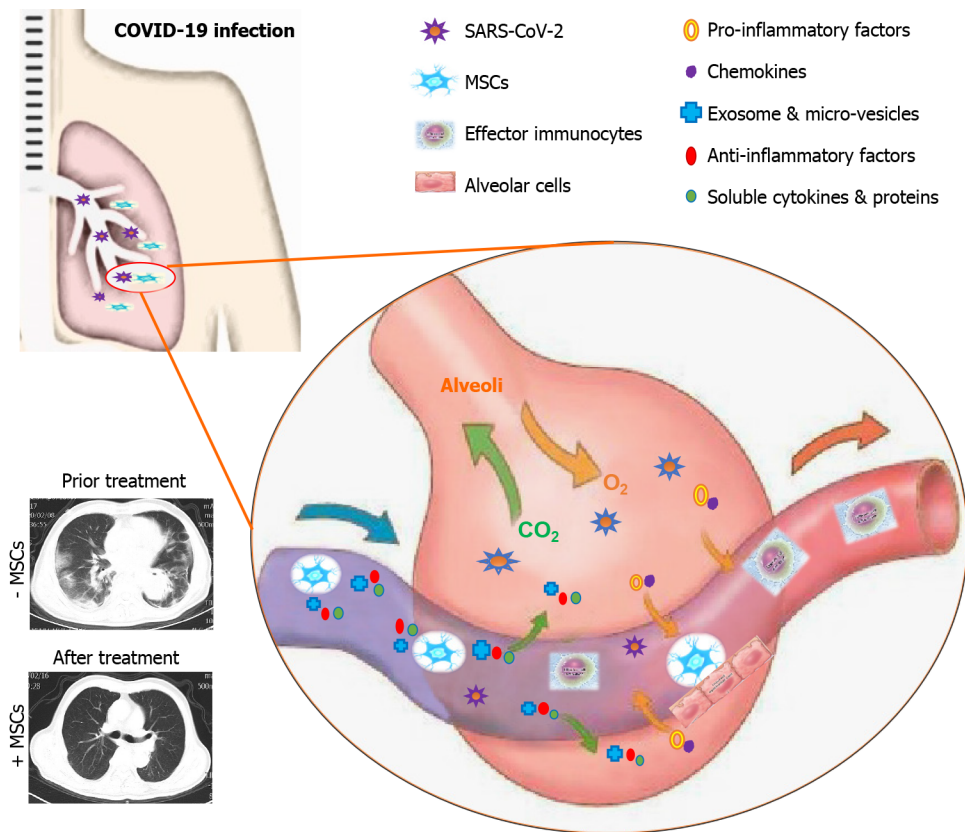


Figure 1 Schematic model for management of coronavirus disease 2019 associated pulmonary disease by mesenchymal stem/stromal cell application. Coronavirus disease 2019 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could result in multifaceted deteriorations of the infected lungs such as ground glass opacity, alveolar epithelial cell injury, inflammatory exudation, pro-inflammatory factor and chemokine accumulation, effector immunocyte abnormalities, and the accompanied cytokine storm. Systematic or partial infusion is adequate for the effective remission of the damaged lung tissues by simultaneously suppressing the abnormal immune response, secreting exosomes and micro-vesicles, and accelerating cell repair and the SARS-CoV-2 clearance. MSCs: Mesenchymal stem/stromal cells; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019.

heparin) should be further optimized and standardized to satisfy the Good Manufacturing Practice (GMP) and quality appraisal guidelines[79]. Third, highly bioactive subpopulations from the heterogeneous MSCs should be identified and generated for different clinical purposes[80]. For instance, we and Stüdle *et al*[80] demonstrated the novel vascular cell adhesion molecule-1⁺ (CD106⁺) UC-MSCs and MSCA-1⁺CD56⁺ BM-MSCs with enhanced chondrogenesis and preferable immunomodulatory property, respectively[19,66,80]. Strikingly, Leng *et al*[10] figured out the superiority of angiotensin-converting enzyme 2 negative subsets in ameliorating the outcomes of patients with COVID-19 pneumonia[10]. Fourth, the stability and repeatability should be improved in generating homogeneous cellular constituents from MSCs for cell-free therapeutic purposes such as the aforementioned EVs and exosomes *via* physical and chemical approaches as well as antigen-binding based enrichment (*e.g.*, CD73, CD105, CD9, and CD63)[54,81]. Additionally, the challenges of establishing appropriate indicators for the systematic and precise evaluation of GMP-grade or clinical grade MSCs and uncovering the detailed molecular mechanisms during preclinical studies are still formidable.

Clinical assessment and administrative management

In the past year, hundreds of millions of people presented with COVID-19 pneumonia and multiple comorbidities, and in particular, the elderly patients and those with severe ALI/ARDS manifested worse outcomes and higher mortality[3,5,82]. Due to the limitation of traditional remedies and the delayed clinical-grade vaccines, pioneering investigators and clinicians turned to the novel MSC-based cytotherapy on the basis of previous experiences upon coronaviruses such as SARS-CoV and MERS-CoV[10,74,83,84]. For instance, Liang *et al*[85] and Leng *et al*[10] reported the favorable prognosis of seven patients with mild and severe COVID-19 with adult tissue-derived MSC administration[10,85]. Subsequently, we further confirmed the efficacious clinical remission in critically ill elderly patients with COVID-19 and multiple comorbidities

The landscape of MSC-based cytotherapy for COVID-19

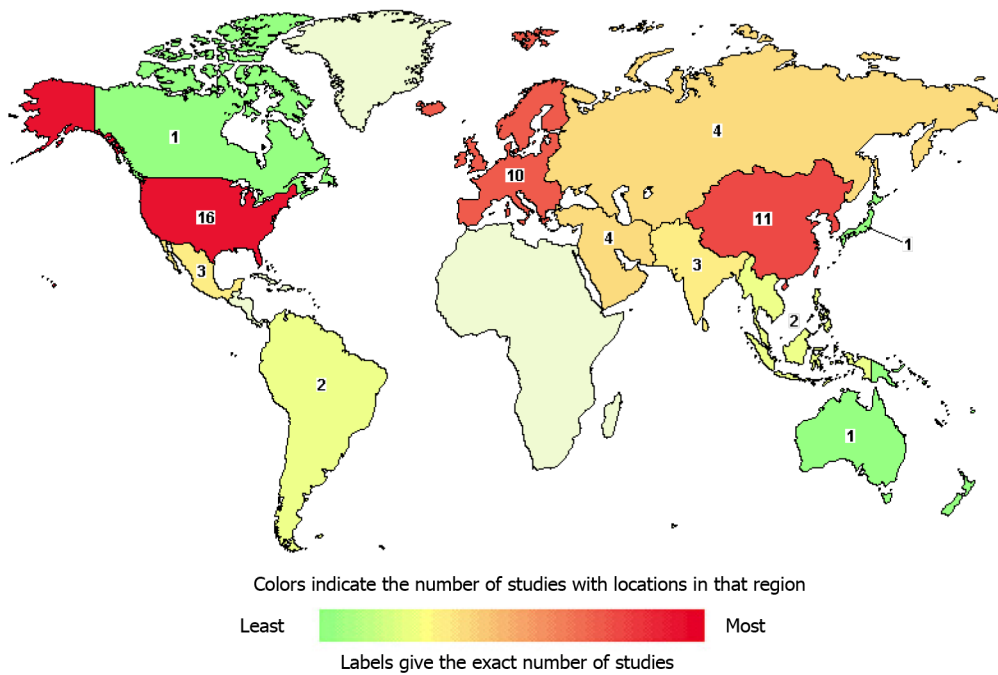


Figure 2 Landscape of mesenchymal stem/stromal cells-based cytotherapy for coronavirus disease 2019. The map reveals the distribution of registered clinical trials on coronavirus disease 2019 treatment with mesenchymal stem/stromal cells with the aid of the Clinicaltrials.gov website.

by systemic infusion of hUC-MSCs[86,87]. Generally, with the aid of MSC administration, the inpatients revealed preferable clinical manifestations without deterioration and secondary infections, including decreased serum bilirubin, effective absorption of infiltration in injured lung tissues, ultimate resumption of the vital signs and blood contents, and sharp decline of pivotal proinflammatory factors, along with the ameliorative status of multiple organ dysfunction syndrome and accompanied multifaceted disease scores and comorbidities (*e.g.*, coronary atherosclerotic heart disease and diabetes)[74,83,88].

According to the ClinicalTrials.gov website, a total of 70 clinical trials focus on MSC-based cytotherapy on COVID-19 pneumonia and ALI/ARDS were registered, which suggested the expectations of clinicians and investigators on MSC-based iateria for improving the therapeutic efficacy for COVID-19 (Figure 2 and Supplementary Table 1). Among them, the United States and China launched 16 and 10 clinical trials, respectively (Figure 3A). Unsurprisingly, most of the registered trials were before the phase 3 stage, which occupied a total proportion of over 90% (Figure 3B). In details, eight interventional trials in China, Turkey, United States, Indonesia, Pakistan, and Russian Federation have finished complete recruitments, which collectively indicates the intriguing perspectives of the ongoing MSC-based therapy in coronavirus infections. Notably, a certain subtype of MSCs and derivate were applied for COVID-19 treatment, such as UC-MSCs, adipose tissue-derived MSCs, dental pulp-derived stem cells, BM-MSCs, and exosomes (Figure 3C). Meanwhile, we found that most of the aforementioned trials focused on ARDS, pneumonia, and cytokine storm, which were the dominating causes of high mortality and morbidity of COVID-19 (Figure 3D).

Despite the inspiring outcomes of the existing prospective studies, the general applicability as well as the latent untoward reactions of the MSC-based cytotherapy for the treatment of large-scale patients hospitalized with COVID-19 should not be neglected[74,83,87,89]. Meanwhile, according to the prevailing international practice, all registered studies ought to follow the principles of Declaration of Helsinki, obtain the informed consent from enrolled cases, and conform to the Centers for Disease Control and Prevention guidelines and World Health Organization recommendation as well[90].

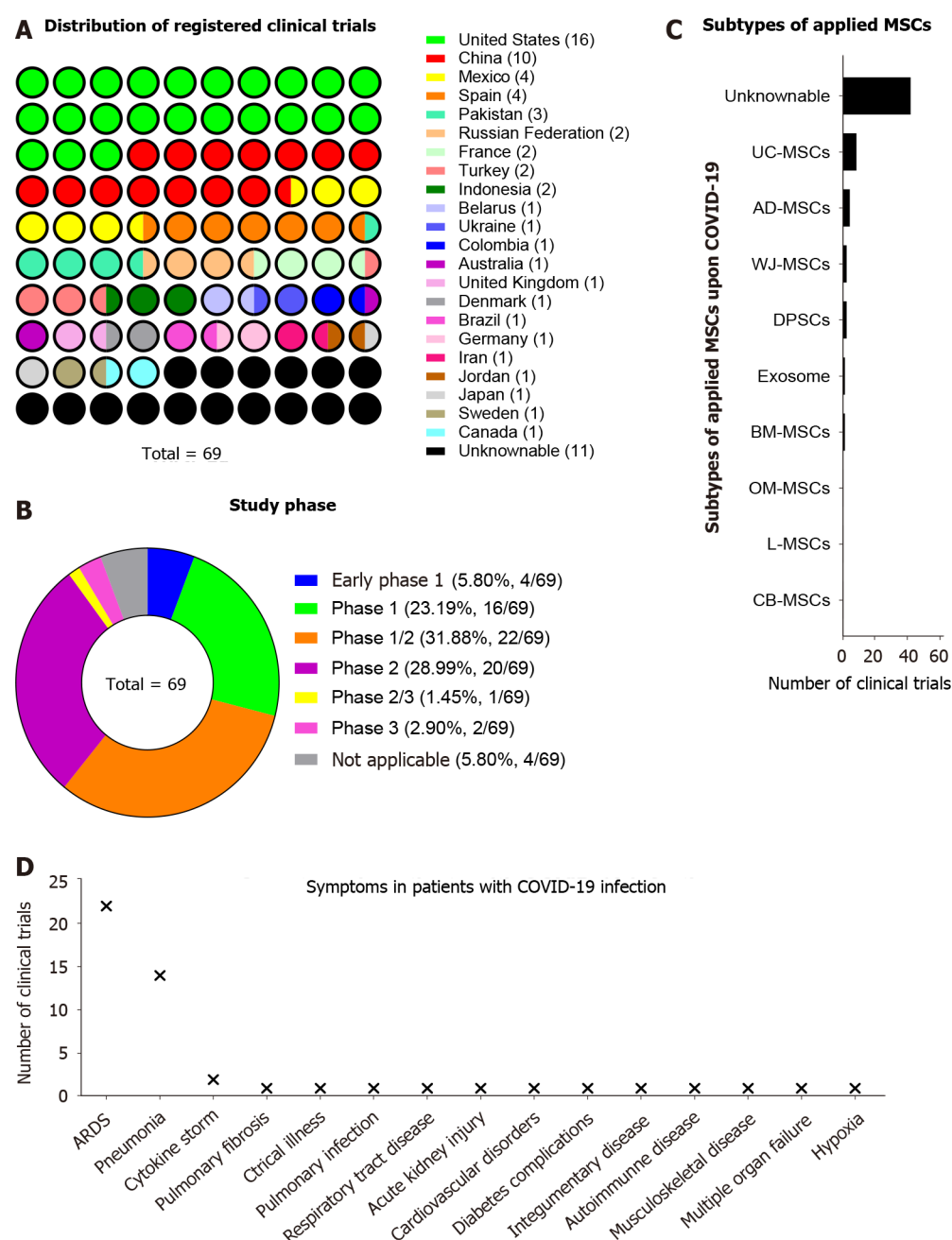


Figure 3 Detailed information of mesenchymal stem/stromal cell-based cytottherapy for coronavirus disease 2019. A: Distribution of registered clinical trials among the countries for coronavirus disease 2019 (COVID-19) treatment by utilizing mesenchymal stem/stromal cell (MSC)-based cytottherapy; B: Study phase of registered clinical trials; C: Distribution of subtypes of applied MSCs for COVID-19 treatment; D: Distribution of symptoms in patients with COVID-19 before MSC-based cytottherapy. MSCs: Mesenchymal stem/stromal cells; COVID-19: Coronavirus disease 2019.

CONCLUSION

Overall, the ongoing COVID-19 triggered by SARS-CoV-2 has become a global pandemic and severely threatened the public security and economic affairs. Patients with COVID-19 and the resultant pulmonary diseases, and in particular, the critical ill type with ALI/ARDS, are inclined to reveal faster disease progression and worse prognosis. Despite the application of multiple traditional remedies, their efficacy is far from satisfaction largely due to the deteriorative cytokine storm and severe pulmonary injury. Herein, on the basis of current progress in the scientific rationale and clinical practice, we systematically review the latest updates and highlight the robust prospect and principles of MSC-based cytottherapy, which would collectively benefit the development of novel comprehensive therapy for COVID-19 associated pulmonary disease management.

REFERENCES

- 1 **Munster VJ**, Koopmans M, van Doremalen N, van Riel D, de Wit E. A Novel Coronavirus Emerging in China - Key Questions for Impact Assessment. *N Engl J Med* 2020; **382**: 692-694 [PMID: [31978293](#) DOI: [10.1056/NEJMp2000929](#)]
- 2 **The Lancet**. Emerging understandings of 2019-nCoV. *Lancet* 2020; **395**: 311 [PMID: [31986259](#) DOI: [10.1016/S0140-6736\(20\)30186-0](#)]
- 3 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: [31986264](#) DOI: [10.1016/S0140-6736\(20\)30183-5](#)]
- 4 **Li Q**, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med* 2020; **382**: 1199-1207 [PMID: [31995857](#) DOI: [10.1056/NEJMoa2001316](#)]
- 5 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: [32007143](#) DOI: [10.1016/S0140-6736\(20\)30211-7](#)]
- 6 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in wuhan, china. *JAMA* 2020; **323**: 1061-1069 [PMID: [32031570](#) DOI: [10.1001/jama.2020.1585](#)]
- 7 **Wang C**, Pan R, Wan X, Tan Y, Xu L, Ho CS, Ho RC. Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. *Int J Environ Res Public Health* 2020; **17** [PMID: [32155789](#) DOI: [10.3390/ijerph17051729](#)]
- 8 Stop the coronavirus stigma now. *Nature* 2020; **580**: 165 [PMID: [32265571](#) DOI: [10.1038/d41586-020-01009-0](#)]
- 9 **Qu W**, Wang Z, Hare JM, Bu G, Mallea JM, Pascual JM, Caplan AI, Kurtzberg J, Zubair AC, Kubrova E, Engelberg-Cook E, Nayfeh T, Shah VP, Hill JC, Wolf ME, Prokop LJ, Murad MH, Sanfilippo FP. Cell-based therapy to reduce mortality from COVID-19: Systematic review and meta-analysis of human studies on acute respiratory distress syndrome. *Stem Cells Transl Med* 2020; **9**: 1007-1022 [PMID: [32472653](#) DOI: [10.1002/scrm.20-0146](#)]
- 10 **Leng Z**, Zhu R, Hou W, Feng Y, Yang Y, Han Q, Shan G, Meng F, Du D, Wang S, Fan J, Wang W, Deng L, Shi H, Li H, Hu Z, Zhang F, Gao J, Liu H, Li X, Zhao Y, Yin K, He X, Gao Z, Wang Y, Yang B, Jin R, Stambler I, Lim LW, Su H, Moskalev A, Cano A, Chakrabarti S, Min KJ, Ellison-Hughes G, Caruso C, Jin K, Zhao RC. Transplantation of ACE2 Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia. *Aging Dis* 2020; **11**: 216-228 [PMID: [32257537](#) DOI: [10.14336/AD.2020.0228](#)]
- 11 **Magagnoli J**, Narendran S, Pereira F, Cummings T, Hardin JW, Sutton SS, Ambati J. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. *medRxiv* 2020; Preprint [PMID: [32511622](#) DOI: [10.1101/2020.04.16.20065920](#)]
- 12 **Samsonraj RM**, Raghunath M, Nurcombe V, Hui JH, van Wijnen AJ, Cool SM. Concise Review: Multifaceted Characterization of Human Mesenchymal Stem Cells for Use in Regenerative Medicine. *Stem Cells Transl Med* 2017; **6**: 2173-2185 [PMID: [29076267](#) DOI: [10.1002/scrm.17-0129](#)]
- 13 **Huo J**, Zhang L, Ren X, Li C, Li X, Dong P, Zheng X, Huang J, Shao Y, Ge M, Zhang J, Wang M, Nie N, Jin P, Zheng Y. Multifaceted characterization of the signatures and efficacy of mesenchymal stem/stromal cells in acquired aplastic anemia. *Stem Cell Res Ther* 2020; **11**: 59 [PMID: [32054519](#) DOI: [10.1186/s13287-020-1577-2](#)]
- 14 **Zhang Y**, Li Y, Li W, Cai J, Yue M, Jiang L, Xu R, Zhang L, Li J, Zhu C. Therapeutic Effect of Human Umbilical Cord Mesenchymal Stem Cells at Various Passages on Acute Liver Failure in Rats. *Stem Cells Int* 2018; **2018**: 7159465 [PMID: [30538751](#) DOI: [10.1155/2018/7159465](#)]
- 15 **El Moshy S**, Radwan IA, Rady D, Abbass MMS, El-Rashidy AA, Sadek KM, Dörfer CE, Fawzy El-Sayed KM. Dental Stem Cell-Derived Secretome/Conditioned Medium: The Future for Regenerative Therapeutic Applications. *Stem Cells Int* 2020; **2020**: 7593402 [PMID: [32089709](#) DOI: [10.1155/2020/7593402](#)]
- 16 **Zhang L**, Wang H, Liu C, Wu Q, Su P, Wu D, Guo J, Zhou W, Xu Y, Shi L, Zhou J. MSX2 Initiates and Accelerates Mesenchymal Stem/Stromal Cell Specification of hPSCs by Regulating TWIST1 and PRAME. *Stem Cell Reports* 2018; **11**: 497-513 [PMID: [30033084](#) DOI: [10.1016/j.stemcr.2018.06.019](#)]
- 17 **Wei Y**, Hou H, Zhang L, Zhao N, Li C, Huo J, Liu Y, Zhang W, Li Z, Liu D, Han Z, Song B, Chi Y. JNKi- and DAC-programmed mesenchymal stem/stromal cells from hESCs facilitate hematopoiesis and alleviate hind limb ischemia. *Stem Cell Res Ther* 2019; **10**: 186 [PMID: [31234947](#) DOI: [10.1186/s13287-019-1302-1](#)]
- 18 **Soontararak S**, Chow L, Johnson V, Coy J, Wheat W, Regan D, Dow S. Mesenchymal Stem Cells (MSC) Derived from Induced Pluripotent Stem Cells (iPSC) Equivalent to Adipose-Derived MSC in

- Promoting Intestinal Healing and Microbiome Normalization in Mouse Inflammatory Bowel Disease Model. *Stem Cells Transl Med* 2018; **7**: 456-467 [PMID: 29635868 DOI: 10.1002/sctm.17-0305]
- 19 **Du W**, Li X, Chi Y, Ma F, Li Z, Yang S, Song B, Cui J, Ma T, Li J, Tian J, Yang Z, Feng X, Chen F, Lu S, Liang L, Han ZB, Han ZC. VCAM-1+ placenta chorionic villi-derived mesenchymal stem cells display potent pro-angiogenic activity. *Stem Cell Res Ther* 2016; **7**: 49 [PMID: 27044487 DOI: 10.1186/s13287-016-0297-0]
 - 20 **Friedenstein AJ**, Petrakova KV, Kurolesova AI, Frolova GP. Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. *Transplantation* 1968; **6**: 230-247 [PMID: 5654088 DOI: 10.1097/00007890-196803000-00009]
 - 21 **Lim M**, Wang W, Liang L, Han ZB, Li Z, Geng J, Zhao M, Jia H, Feng J, Wei Z, Song B, Zhang J, Li J, Liu T, Wang F, Li T, Fang Y, Gao J, Han Z. Intravenous injection of allogeneic umbilical cord-derived multipotent mesenchymal stromal cells reduces the infarct area and ameliorates cardiac function in a porcine model of acute myocardial infarction. *Stem Cell Res Ther* 2018; **9**: 129 [PMID: 29751831 DOI: 10.1186/s13287-018-0888-z]
 - 22 **Weiss DJ**, Casaburi R, Flannery R, LeRoux-Williams M, Tashkin DP. A placebo-controlled, randomized trial of mesenchymal stem cells in COPD. *Chest* 2013; **143**: 1590-1598 [PMID: 23172272 DOI: 10.1378/chest.12-2094]
 - 23 **Zhao Q**, Zhang L, Wei Y, Yu H, Zou L, Huo J, Yang H, Song B, Wei T, Wu D, Zhang W, Liu D, Li Z, Chi Y, Han Z. Systematic comparison of hUC-MSCs at various passages reveals the variations of signatures and therapeutic effect on acute graft-versus-host disease. *Stem Cell Res Ther* 2019; **10**: 354 [PMID: 31779707 DOI: 10.1186/s13287-019-1478-4]
 - 24 **Cho J**, D'Antuono M, Glicksman M, Wang J, Jonklaas J. A review of clinical trials: mesenchymal stem cell transplant therapy in type 1 and type 2 diabetes mellitus. *Am J Stem Cells* 2018; **7**: 82-93 [PMID: 30510843]
 - 25 **Monsel A**, Zhu YG, Gennai S, Hao Q, Hu S, Rouby JJ, Rosenzweig M, Matthay MA, Lee JW. Therapeutic Effects of Human Mesenchymal Stem Cell-derived Microvesicles in Severe Pneumonia in Mice. *Am J Respir Crit Care Med* 2015; **192**: 324-336 [PMID: 26067592 DOI: 10.1164/rccm.201410-1765OC]
 - 26 **Bouvier NM**, Lowen AC. Animal Models for Influenza Virus Pathogenesis and Transmission. *Viruses* 2010; **2**: 1530-1563 [PMID: 21442033 DOI: 10.3390/v20801530]
 - 27 **Fukushi M**, Ito T, Oka T, Kitazawa T, Miyoshi-Akiyama T, Kirikae T, Yamashita M, Kudo K. Serial histopathological examination of the lungs of mice infected with influenza A virus PR8 strain. *PLoS One* 2011; **6**: e21207 [PMID: 21701593 DOI: 10.1371/journal.pone.0021207]
 - 28 **Khatrri M**, Richardson LA, Meulia T. Mesenchymal stem cell-derived extracellular vesicles attenuate influenza virus-induced acute lung injury in a pig model. *Stem Cell Res Ther* 2018; **9**: 17 [PMID: 29378639 DOI: 10.1186/s13287-018-0774-8]
 - 29 **Sun J**, Han ZB, Liao W, Yang SG, Yang Z, Yu J, Meng L, Wu R, Han ZC. Intrapulmonary delivery of human umbilical cord mesenchymal stem cells attenuates acute lung injury by expanding CD4+CD25+ Forkhead Boxp3 (FOXP3)+ regulatory T cells and balancing anti- and pro-inflammatory factors. *Cell Physiol Biochem* 2011; **27**: 587-596 [PMID: 21691076 DOI: 10.1159/000329980]
 - 30 **Rojas M**, Cárdenes N, Kocyildirim E, Tedrow JR, Cáceres E, Deans R, Ting A, Bermúdez C. Human adult bone marrow-derived stem cells decrease severity of lipopolysaccharide-induced acute respiratory distress syndrome in sheep. *Stem Cell Res Ther* 2014; **5**: 42 [PMID: 24670268 DOI: 10.1186/srct430]
 - 31 **Hao Q**, Zhu YG, Monsel A, Gennai S, Lee T, Xu F, Lee JW. Study of Bone Marrow and Embryonic Stem Cell-Derived Human Mesenchymal Stem Cells for Treatment of Escherichia coli Endotoxin-Induced Acute Lung Injury in Mice. *Stem Cells Transl Med* 2015; **4**: 832-840 [PMID: 25999518 DOI: 10.5966/sctm.2015-0006]
 - 32 **Horie S**, Masterson C, Devaney J, Laffey JG. Stem cell therapy for acute respiratory distress syndrome: a promising future? *Curr Opin Crit Care* 2016; **22**: 14-20 [PMID: 26645555 DOI: 10.1097/MCC.0000000000000276]
 - 33 **D'Alessio FR**. Mouse Models of Acute Lung Injury and ARDS. *Methods Mol Biol* 2018; **1809**: 341-350 [PMID: 29987799 DOI: 10.1007/978-1-4939-8570-8_22]
 - 34 **Yu F**, Du L, Ojcius DM, Pan C, Jiang S. Measures for diagnosing and treating infections by a novel coronavirus responsible for a pneumonia outbreak originating in Wuhan, China. *Microbes Infect* 2020; **22**: 74-79 [PMID: 32017984 DOI: 10.1016/j.micinf.2020.01.003]
 - 35 **Bauer TT**, Ewig S, Rodloff AC, Müller EE. Acute respiratory distress syndrome and pneumonia: a comprehensive review of clinical data. *Clin Infect Dis* 2006; **43**: 748-756 [PMID: 16912951 DOI: 10.1086/506430]
 - 36 **Zheng G**, Huang L, Tong H, Shu Q, Hu Y, Ge M, Deng K, Zhang L, Zou B, Cheng B, Xu J. Treatment of acute respiratory distress syndrome with allogeneic adipose-derived mesenchymal stem cells: a randomized, placebo-controlled pilot study. *Respir Res* 2014; **15**: 39 [PMID: 24708472 DOI: 10.1186/1465-9921-15-39]
 - 37 **Wilson JG**, Liu KD, Zhuo H, Caballero L, McMillan M, Fang X, Cosgrove K, Vojnik R, Calfee CS, Lee JW, Rogers AJ, Levitt J, Wiener-Kronish J, Bajwa EK, Leavitt A, McKenna D, Thompson BT, Matthay MA. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. *Lancet Respir Med* 2015; **3**: 24-32 [PMID: 25529339 DOI: 10.1016/S2213-2600(14)70291-7]
 - 38 **Zhang GY**, Liao T, Zhou SB, Fu XB, Li QF. Mesenchymal stem (stromal) cells for treatment of

- acute respiratory distress syndrome. *Lancet Respir Med* 2015; **3**: e11-e12 [PMID: 25890654 DOI: 10.1016/S2213-2600(15)00049-1]
- 39 **Matthay MA**, Calfee CS, Zhuo H, Thompson BT, Wilson JG, Levitt JE, Rogers AJ, Gotts JE, Wiener-Kronish JP, Bajwa EK, Donahoe MP, McVerry BJ, Ortiz LA, Exline M, Christman JW, Abbott J, Delucchi KL, Caballero L, McMillan M, McKenna DH, Liu KD. Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): a randomised phase 2a safety trial. *Lancet Respir Med* 2019; **7**: 154-162 [PMID: 30455077 DOI: 10.1016/S2213-2600(18)30418-1]
 - 40 **Ni K**, Liu M, Zheng J, Wen L, Chen Q, Xiang Z, Lam KT, Liu Y, Chan GC, Lau YL, Tu W. PD-1/PD-L1 Pathway Mediates the Alleviation of Pulmonary Fibrosis by Human Mesenchymal Stem Cells in Humanized Mice. *Am J Respir Cell Mol Biol* 2018; **58**: 684-695 [PMID: 29220578 DOI: 10.1165/rcmb.2017-0326OC]
 - 41 **Bouros D**. Pirfenidone for idiopathic pulmonary fibrosis. *Lancet* 2011; **377**: 1727-1729 [PMID: 21571363 DOI: 10.1016/S0140-6736(11)60546-1]
 - 42 **Wynn TA**, Ramalingam TR. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. *Nat Med* 2012; **18**: 1028-1040 [PMID: 22772564 DOI: 10.1038/nm.2807]
 - 43 **Liu M**, Ren D, Wu D, Zheng J, Tu W. Stem Cell and Idiopathic Pulmonary Fibrosis: Mechanisms and Treatment. *Curr Stem Cell Res Ther* 2015; **10**: 466-476 [PMID: 25986617 DOI: 10.2174/1574888x10666150519092639]
 - 44 **Chambers DC**, Enever D, Ilic N, Sparks L, Whitelaw K, Ayres J, Yerkovich ST, Khalil D, Atkinson KM, Hopkins PM. A phase 1b study of placenta-derived mesenchymal stromal cells in patients with idiopathic pulmonary fibrosis. *Respirology* 2014; **19**: 1013-1018 [PMID: 25039426 DOI: 10.1111/resp.12343]
 - 45 **Behnke J**, Kremer S, Shahzad T, Chao CM, Böttcher-Friebertshäuser E, Morty RE, Bellusci S, Ehrhardt H. MSC Based Therapies-New Perspectives for the Injured Lung. *J Clin Med* 2020; **9** [PMID: 32138309 DOI: 10.3390/jcm9030682]
 - 46 **Krause DS**, Theise ND, Collector MI, Henegariu O, Hwang S, Gardner R, Neutzel S, Sharkis SJ. Multi-organ, multi-lineage engraftment by a single bone marrow-derived stem cell. *Cell* 2001; **105**: 369-377 [PMID: 11348593 DOI: 10.1016/S0092-8674(01)00328-2]
 - 47 **Ortiz LA**, Gambelli F, McBride C, Gaupp D, Baddoo M, Kaminski N, Phinney DG. Mesenchymal stem cell engraftment in lung is enhanced in response to bleomycin exposure and ameliorates its fibrotic effects. *Proc Natl Acad Sci USA* 2003; **100**: 8407-8411 [PMID: 12815096 DOI: 10.1073/pnas.1432929100]
 - 48 **Akram KM**, Samad S, Spiteri MA, Forsyth NR. Mesenchymal stem cells promote alveolar epithelial cell wound repair *in vitro* through distinct migratory and paracrine mechanisms. *Respir Res* 2013; **14**: 9 [PMID: 23350749 DOI: 10.1186/1465-9921-14-9]
 - 49 **Yew TL**, Hung YT, Li HY, Chen HW, Chen LL, Tsai KS, Chiou SH, Chao KC, Huang TF, Chen HL, Hung SC. Enhancement of wound healing by human multipotent stromal cell conditioned medium: The paracrine factors and p38 mapk activation. *Cell Transplant* 2011; **20**: 693-706 [PMID: 21176394 DOI: 10.3727/096368910X550198]
 - 50 **Huh JW**, Kim SY, Lee JH, Lee JS, Van Ta Q, Kim M, Oh YM, Lee YS, Lee SD. Bone marrow cells repair cigarette smoke-induced emphysema in rats. *Am J Physiol Lung Cell Mol Physiol* 2011; **301**: L255-L266 [PMID: 21622846 DOI: 10.1152/ajplung.00253.2010]
 - 51 **Li J**, Huang S, Zhang J, Feng C, Gao D, Yao B, Wu X, Fu X. Mesenchymal stem cells ameliorate inflammatory cytokine-induced impairment of AT-II cells through a keratinocyte growth factor-dependent PI3K/Akt/mTOR signaling pathway. *Mol Med Rep* 2016; **13**: 3755-3762 [PMID: 27035760 DOI: 10.3892/mmr.2016.5004]
 - 52 **Baglio SR**, Rooijers K, Koppers-Lalic D, Verweij FJ, Pérez Lanzón M, Zini N, Naaijken B, Perut F, Niessen HW, Baldini N, Pegtel DM. Human bone marrow- and adipose-mesenchymal stem cells secrete exosomes enriched in distinctive miRNA and tRNA species. *Stem Cell Res Ther* 2015; **6**: 127 [PMID: 26129847 DOI: 10.1186/s13287-015-0116-z]
 - 53 **Eirin A**, Zhu XY, Puranik AS, Woollard JR, Tang H, Dasari S, Lerman A, van Wijnen AJ, Lerman LO. Integrated transcriptomic and proteomic analysis of the molecular cargo of extracellular vesicles derived from porcine adipose tissue-derived mesenchymal stem cells. *PLoS One* 2017; **12**: e0174303 [PMID: 28333993 DOI: 10.1371/journal.pone.0174303]
 - 54 **Miao W**, Song B, Shi B, Wan Q, Lv Q, Chen H, Zhu M, Zhang L, Han Y, Wu D. Immune thrombocytopenia plasma-derived exosomes impaired megakaryocyte and platelet production through an apoptosis pathway. *Thromb Haemost* 2021; **121**: 495-505 [PMID: 33124021 DOI: 10.1055/s-0040-1718761]
 - 55 **Weiss DJ**. Stem cells, cell therapies, and bioengineering in lung biology and diseases. Comprehensive review of the recent literature 2010-2012. *Ann Am Thorac Soc* 2013; **10**: S45-S97 [PMID: 23869446 DOI: 10.1513/AnnalsATS.201304-090AW]
 - 56 **Lee JW**, Fang X, Krasnodembskaya A, Howard JP, Matthay MA. Concise review: Mesenchymal stem cells for acute lung injury: role of paracrine soluble factors. *Stem Cells* 2011; **29**: 913-919 [PMID: 21506195 DOI: 10.1002/stem.643]
 - 57 **Lee JW**, Fang X, Gupta N, Serikov V, Matthay MA. Allogeneic human mesenchymal stem cells for treatment of E. coli endotoxin-induced acute lung injury in the *ex vivo* perfused human lung. *Proc Natl Acad Sci USA* 2009; **106**: 16357-16362 [PMID: 19721001 DOI: 10.1073/pnas.0907996106]
 - 58 **Zhu YG**, Feng XM, Abbott J, Fang XH, Hao Q, Monsel A, Qu JM, Matthay MA, Lee JW. Human

- mesenchymal stem cell microvesicles for treatment of Escherichia coli endotoxin-induced acute lung injury in mice. *Stem Cells* 2014; **32**: 116-125 [PMID: [23939814](#) DOI: [10.1002/stem.1504](#)]
- 59 **Fang X**, Neyrinck AP, Matthay MA, Lee JW. Allogeneic human mesenchymal stem cells restore epithelial protein permeability in cultured human alveolar type II cells by secretion of angiopoietin-1. *J Biol Chem* 2010; **285**: 26211-26222 [PMID: [20554518](#) DOI: [10.1074/jbc.M110.119917](#)]
- 60 **Tang XD**, Shi L, Monsel A, Li XY, Zhu HL, Zhu YG, Qu JM. Mesenchymal Stem Cell Microvesicles Attenuate Acute Lung Injury in Mice Partly Mediated by Ang-1 mRNA. *Stem Cells* 2017; **35**: 1849-1859 [PMID: [28376568](#) DOI: [10.1002/stem.2619](#)]
- 61 **Krasnodembskaya A**, Song Y, Fang X, Gupta N, Serikov V, Lee JW, Matthay MA. Antibacterial effect of human mesenchymal stem cells is mediated in part from secretion of the antimicrobial peptide LL-37. *Stem Cells* 2010; **28**: 2229-2238 [PMID: [20945332](#) DOI: [10.1002/stem.544](#)]
- 62 **Islam MN**, Das SR, Emin MT, Wei M, Sun L, Westphalen K, Rowlands DJ, Quadri SK, Bhattacharya S, Bhattacharya J. Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury. *Nat Med* 2012; **18**: 759-765 [PMID: [22504485](#) DOI: [10.1038/nm.2736](#)]
- 63 **Ahn SY**, Park WS, Kim YE, Sung DK, Sung SI, Ahn JY, Chang YS. Vascular endothelial growth factor mediates the therapeutic efficacy of mesenchymal stem cell-derived extracellular vesicles against neonatal hyperoxic lung injury. *Exp Mol Med* 2018; **50**: 1-12 [PMID: [29650962](#) DOI: [10.1038/s12276-018-0055-8](#)]
- 64 **Reiter J**, Drummond S, Sammour I, Huang J, Florea V, Dornas P, Hare JM, Rodrigues CO, Young KC. Stromal derived factor-1 mediates the lung regenerative effects of mesenchymal stem cells in a rodent model of bronchopulmonary dysplasia. *Respir Res* 2017; **18**: 137 [PMID: [28701189](#) DOI: [10.1186/s12931-017-0620-z](#)]
- 65 **Muppala S**, Xiao R, Krukovets I, Verbovetsky D, Yendamuri R, Habib N, Raman P, Plow E, Stenina-Adognravi O. Thrombospondin-4 mediates TGF- β -induced angiogenesis. *Oncogene* 2017; **36**: 5189-5198 [PMID: [28481870](#) DOI: [10.1038/onc.2017.140](#)]
- 66 **Wei Y**, Zhang L, Chi Y, Ren X, Gao Y, Song B, Li C, Han Z. High-efficient generation of vcam-1(+) mesenchymal stem cells with multidimensional superiorities in signatures and efficacy on aplastic anaemia mice. *Cell Prolif* 2020; **53**: e12862 [PMID: [32597552](#) DOI: [10.1111/cpr.12862](#)]
- 67 **Sagaradze GD**, Basalova NA, Efimenko AY, Tkachuk VA. Mesenchymal Stromal Cells as Critical Contributors to Tissue Regeneration. *Front Cell Dev Biol* 2020; **8**: 576176 [PMID: [33102483](#) DOI: [10.3389/fcell.2020.576176](#)]
- 68 **Wang L**, Zhang L, Liang X, Zou J, Liu N, Liu T, Wang G, Ding X, Liu Y, Zhang B, Liang R, Wang S. Adipose Tissue-Derived Stem Cells from Type 2 Diabetics Reveal Conservative Alterations in Multidimensional Characteristics. *Int J Stem Cells* 2020; **13**: 268-278 [PMID: [32587133](#) DOI: [10.15283/ijsc20028](#)]
- 69 **Zhang L**, Wei Y, Chi Y, Liu D, Yang S, Han Z, Li Z. Two-step generation of mesenchymal stem/stromal cells from human pluripotent stem cells with reinforced efficacy upon osteoarthritis rabbits by HA hydrogel. *Cell Biosci* 2021; **11**: 6 [PMID: [33407870](#) DOI: [10.1186/s13578-020-00516-x](#)]
- 70 **Menasché P**. Cell therapy trials for heart regeneration - lessons learned and future directions. *Nat Rev Cardiol* 2018; **15**: 659-671 [PMID: [29743563](#) DOI: [10.1038/s41569-018-0013-0](#)]
- 71 **Hou H**, Zhang L, Duan L, Liu Y, Han Z, Li Z, Cao X. Spatio-temporal metabolokinetics and efficacy of human placenta-derived mesenchymal stem/stromal cells on mice with refractory crohn's-like enterocutaneous fistula. *Stem Cell Rev Rep* 2020; **16**: 1292-1304 [PMID: [33011925](#) DOI: [10.1007/s12015-020-10053-2](#)]
- 72 **Lin BL**, Chen JF, Qiu WH, Wang KW, Xie DY, Chen XY, Liu QL, Peng L, Li JG, Mei YY, Weng WZ, Peng YW, Cao HJ, Xie JQ, Xie SB, Xiang AP, Gao ZL. Allogeneic bone marrow-derived mesenchymal stromal cells for hepatitis B virus-related acute-on-chronic liver failure: A randomized controlled trial. *Hepatology* 2017; **66**: 209-219 [PMID: [28370357](#) DOI: [10.1002/hep.29189](#)]
- 73 **Kitadate Y**, Jörg DJ, Tokue M, Maruyama A, Ichikawa R, Tsuchiya S, Segi-Nishida E, Nakagawa T, Uchida A, Kimura-Yoshida C, Mizuno S, Sugiyama F, Azami T, Ema M, Noda C, Kobayashi S, Matsuo I, Kanai Y, Nagasawa T, Sugimoto Y, Takahashi S, Simons BD, Yoshida S. Competition for Mitogens Regulates Spermatogenic Stem Cell Homeostasis in an Open Niche. *Cell Stem Cell* 2019; **24**: 79-92.e6 [PMID: [30581080](#) DOI: [10.1016/j.stem.2018.11.013](#)]
- 74 **Golchin A**, Seyedjafari E, Ardeshtyrlajimi A. Mesenchymal stem cell therapy for covid-19: Present or future. *Stem Cell Rev Rep* 2020; **16**: 427-433 [PMID: [32281052](#) DOI: [10.1007/s12015-020-09973-w](#)]
- 75 **Hough RF**, Islam MN, Gusarova GA, Jin G, Das S, Bhattacharya J. Endothelial mitochondria determine rapid barrier failure in chemical lung injury. *JCI Insight* 2019; **4** [PMID: [30728333](#) DOI: [10.1172/jci.insight.124329](#)]
- 76 **Loibl M**, Wuertz-Kozak K, Vadala G, Lang S, Fairbank J, Urban JP. Controversies in regenerative medicine: Should intervertebral disc degeneration be treated with mesenchymal stem cells? *JOR Spine* 2019; **2**: e1043 [PMID: [31463457](#) DOI: [10.1002/jsp2.1043](#)]
- 77 **Kern S**, Eichler H, Stoeve J, Klüter H, Bieback K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. *Stem Cells* 2006; **24**: 1294-1301 [PMID: [16410387](#) DOI: [10.1634/stemcells.2005-0342](#)]
- 78 **Chatzistamatiou TK**, Papassavas AC, Michalopoulos E, Gamaloutsos C, Mallis P, Gontika I, Panagoulis E, Koussoulakos SL, Stavropoulos-Giokas C. Optimizing isolation culture and freezing

- methods to preserve Wharton's jelly's mesenchymal stem cell (MSC) properties: an MSC banking protocol validation for the Hellenic Cord Blood Bank. *Transfusion* 2014; **54**: 3108-3120 [PMID: 24894363 DOI: 10.1111/trf.12743]
- 79 **Van Pham P**, Truong NC, Le PT, Tran TD, Vu NB, Bui KH, Phan NK. Isolation and proliferation of umbilical cord tissue derived mesenchymal stem cells for clinical applications. *Cell Tissue Bank* 2016; **17**: 289-302 [PMID: 26679929 DOI: 10.1007/s10561-015-9541-6]
 - 80 **Stüdle C**, Occhetta P, Geier F, Mehrkens A, Barbero A, Martin I. Challenges Toward the Identification of Predictive Markers for Human Mesenchymal Stromal Cells Chondrogenic Potential. *Stem Cells Transl Med* 2019; **8**: 194-204 [PMID: 30676001 DOI: 10.1002/sctm.18-0147]
 - 81 **Eirin A**, Zhu XY, Puranik AS, Woollard JR, Tang H, Dasari S, Lerman A, van Wijnen AJ, Lerman LO. Comparative proteomic analysis of extracellular vesicles isolated from porcine adipose tissue-derived mesenchymal stem/stromal cells. *Sci Rep* 2016; **6**: 36120 [PMID: 27786293 DOI: 10.1038/srep36120]
 - 82 **Promptchara E**, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol* 2020; **38**: 1-9 [PMID: 32105090 DOI: 10.12932/AP-200220-0772]
 - 83 **Meng F**, Xu R, Wang S, Xu Z, Zhang C, Li Y, Yang T, Shi L, Fu J, Jiang T, Huang L, Zhao P, Yuan X, Fan X, Zhang JY, Song J, Zhang D, Jiao Y, Liu L, Zhou C, Maeurer M, Zumla A, Shi M, Wang FS. Human umbilical cord-derived mesenchymal stem cell therapy in patients with COVID-19: a phase 1 clinical trial. *Signal Transduct Target Ther* 2020; **5**: 172 [PMID: 32855385 DOI: 10.1038/s41392-020-00286-5]
 - 84 **Amanat F**, Krammer F. SARS-CoV-2 Vaccines: Status Report. *Immunity* 2020; **52**: 583-589 [PMID: 32259480 DOI: 10.1016/j.immuni.2020.03.007]
 - 85 **Liang B**, Chen J, Li T, Wu H, Yang W, Li Y, Li J, Yu C, Nie F, Ma Z, Yang M, Xiao M, Nie P, Gao Y, Qian C, Hu M. Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells: A case report. *Medicine (Baltimore)* 2020; **99**: e21429 [PMID: 32756149 DOI: 10.1097/MD.00000000000021429]
 - 86 **Wang L**, Liu T, Liang R, Wang G, Liu Y, Zou J, Liu N, Zhang B, Ding X, Cai X, Wang Z, Xu X, Ricordi C, Wang S, Shen Z. Mesenchymal stem cells ameliorate β cell dysfunction of human type 2 diabetic islets by reversing β cell dedifferentiation. *EBioMedicine* 2020; **51**: 102615 [PMID: 31918404 DOI: 10.1016/j.ebiom.2019.102615]
 - 87 **Zhang L**, Zou L, Ma Y, Feng C, Zhan R, Yang H, Song B, Han Z. Multifaceted modifications for a cell size-based circulating tumor cell scope technique hold the prospect for large-scale application in general populations. *Cell Biol Int* 2021; **45**: 345-357 [PMID: 33085139 DOI: 10.1002/cbin.11491]
 - 88 **Rizwan K**, Rasheed T, Khan SA, Bilal M, Mahmood T. Current perspective on diagnosis, epidemiological assessment, prevention strategies, and potential therapeutic interventions for severe acute respiratory infections caused by 2019 novel coronavirus (SARS-CoV-2). *Hum Vaccin Immunother* 2020; **16**: 3001-3010 [PMID: 32881628 DOI: 10.1080/21645515.2020.1794684]
 - 89 **Zumla A**, Wang FS, Ippolito G, Petrosillo N, Agrati C, Azhar EI, Chang C, El-Kafrawy SA, Osman M, Zitzvogel L, Galle PR, Locatelli F, Gorman E, Cordon-Cardo C, O'Kane C, McAuley D, Maeurer M. Reducing mortality and morbidity in patients with severe COVID-19 disease by advancing ongoing trials of Mesenchymal Stromal (stem) Cell (MSC) therapy - Achieving global consensus and visibility for cellular host-directed therapies. *Int J Infect Dis* 2020; **96**: 431-439 [PMID: 32425638 DOI: 10.1016/j.ijid.2020.05.040]
 - 90 **Rogers CJ**, Harman RJ, Bunnell BA, Schreiber MA, Xiang C, Wang FS, Santidrian AF, Minev BR. Rationale for the clinical use of adipose-derived mesenchymal stem cells for COVID-19 patients. *J Transl Med* 2020; **18**: 203 [PMID: 32423449 DOI: 10.1186/s12967-020-02380-2]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

