

New Treatments (MSC) in Immune Disorders Like Cancers and Covid Infection: Cancer and Virus New Treatment (MSC)

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Abstract

The recent coronavirus disease 2019 outbreak and viral infections around the world has had an enormous impact on the global health burden, threatening the lives of many individuals, spatially with underlying disease like cancerous patients and has had severe socio-economic consequences. Many pharmaceutical and biotechnology companies have commenced intensive research on different therapeutic strategies, from repurposed antiviral drugs to vaccines and monoclonal antibodies to prevent the spread of the disease and treat infected patients. Among the various strategies, advanced therapeutic approaches including cell- and gene-editing-based therapeutics are also being investigated, and initial results in in-vitro and early phase I studies have been promising. However, further assessments are required. This article reviews the underlying mechanisms for the pathogenesis of, and discusses available therapeutic candidates and advanced modalities that are being evaluated and used for treatment for immune deficient patients in cancers and viruses infected.

Keywords: Stem cell- immune system- cancer- virus- covid-19- New treatment- Infection

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Regenerative Medicine therapeutics

Novel coronavirus disease has attracted much attention around the world due to its rapid transmission among humans and relatively high mortality rate. Studies are increasing to find the best therapeutic approach for the disease and its management. Regenerative medicine offers various cell-tissue therapeutics and related products, such as stem cell therapy, natural killer (NK) cell therapy, Chimeric antigen receptor (CAR) T cell therapy, exosomes, and tissue products. Interestingly, mesenchymal stem cells (MSCs) can reduce inflammatory symptoms and protect against cytokine storm, which critically contributes to the COVID-19 progression. Notably, having the potentials to exert cytotoxic effects on infected cells and induce interferon production probably make NK cells a candidate for COVID-19 cell therapy. Besides, exosomes are one of the crucial products of cells that can exert therapeutic effects through the induction of immune responses and neutralizing antibody titers.

The paper aims to briefly consider current options for COVID-19 therapy to show that there is no specific cure for COVID-19, and then assess the real opportunities and range of promises regenerative medicine can provide for specific treatment of COVID.

With the outbreak of coronavirus disease caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) especially in immunocompromised like cancers patients, the world had been facing an unprecedented challenge. Considering the lack of appropriate therapy for COVID-19, it is crucial to develop effective treatments instead of supportive approaches. Mesenchymal stem cells (MSCs) as multipotent stromal cells have been shown to possess treating potency through inhibiting or modulating the pathological events in COVID-19. MSCs and their exosomes participate in immunomodulation by controlling cell-mediated immunity and cytokine release [1-3]. Furthermore, they

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repair the renin-angiotensin-aldosterone system (RAAS) malfunction, increase alveolar fluid clearance, and reduce the chance of hypercoagulation. Besides the lung, which is the primary target of SARS-CoV-2, the heart, kidney, nervous system, and gastrointestinal tract are also affected by COVID-19 [4]. Thus, the efficacy of targeting these organs via different delivery routes of MSCs and their exosomes should be evaluated to ensure safe and effective MSCs administration in COVID-19. This review focuses on the proposed therapeutic mechanisms and delivery routes of MSCs and their exosomes to the damaged organs. It also discusses the possible application of primed and genetically modified MSCs as a promising drug delivery system in COVID-19 [5]. Moreover, the recent advances in the clinical trials of MSCs and MSCs-derived exosomes as one of the promising therapeutic approaches in COVID-19 have been reviewed [6].

Regenerative medicine (RM) is an interdisciplinary field that uses different approaches to accelerate the repair and regeneration or replace damaged or diseased human cells or tissues to achieve normal tissue function. These approaches include the stimulation of the body's own repair processes, transplantation of progenitor cells, stem cells, or tissues, as well as the use of cells and exosomes as delivery-vehicles for cytokines, genes, or other therapeutic agents [7, 8]. COVID-19 pneumonia is a specific disease consistent with diffuse alveolar damage resulting in severe hypoxemia. Therefore, the most serious cause of death from COVID-19 is lung dysfunction [9]. Here, we consider RM approaches to cure COVID-19 pneumonia based on what RM has so far used to treat lung diseases, injuries, or pneumonia induced by other pathogens. These approaches include stem and progenitor cell transplantation, stem cell-derived exosomes, and microRNAs therapy [10]. There are no approved and effective therapeutics against COVID-19, and scientists are grappling with time to find effective treatments and vaccines. Cell-induced therapies using stem cells, particularly mesenchymal stem cells (MSCs), have been a primary target of therapeutic studies. MSCs are self-renewing multipotent stem cells that can differentiate into several cell types [11]. They represent a promising therapy for several chronic lung diseases with high fatality and morbidity rates, such as chronic obstructive pulmonary disease (COPD), obstructive bronchiolitis, idiopathic pulmonary fibrosis, and acute respiratory distress syndrome (ARDS) [12].

Immunomodulation with MSC

MSCs are considered the only stem cell type with immunomodulatory activity and are, therefore, a primary target for therapeutic development for autoimmune disease and inflammation. MSCs secrete immunomodulators, including chemokines, IL-6 and prostaglandin E2 (PGE2), hemoxygenase-1, leukocyte inhibitory factor, indolamine 2,3-dioxygenase (IDO), and transforming growth factor β [45]. MSCs also induce IL-10 expression [13]. Human umbilical cord tissue-derived MSCs (hUC-MSCs) reprogram macrophages and monocytes via cytoplasmic organelles (RNA processing bodies [p-bodies]), a critical lung inflammatory inhibitor. These p-bodies are engulfed

by macrophages and monocytes, modulating transcription and inhibiting T cell activation. Low-density lipoprotein receptor-related proteins mediate this interaction on the surface of macrophages and monocytes while blocking pharmacological inhibitors. These findings provide new insight into the inflammatory modulation of MSCs without long-term engulfment by indirectly inhibiting the T cell response through monocyte and macrophage reprogramming by p-bodies [14, 15]. MSCs can migrate to injured and affected tissue. In lung injury, ARDS, and sepsis, MSCs migrate to and are trapped in the lungs, promoting secretion of antimicrobial agents, cytokines, and growth factors [16]. MSC is a preferred acronym that stands for a population of multipotent stem/progenitor cells, commonly known as mesenchymal stem cells, mesenchymal stromal cells, multipotent stromal cells, and mesenchymal progenitor cells. MSCs can be isolated from various tissue sources, such as bone marrow, adipose tissue, peripheral blood, placenta, umbilical cord, amniotic fluid, and gingival tissues [17]. They also have the excellent proliferative capability, and an intrinsic differentiation potential that has not been found in any other natural cell types⁵². MSC infusion into human patients begun since the year 1993 and has been reported as early as in 1995⁵³. Since then, during the past 25 years, MSC infusion has exhibited an excellent safety profile in over 950 registered clinical trials and with over 10,000 patients, treated in a clinical setting⁵². MSC has powerful immunomodulatory and endogenous repair and regenerative properties. In the past, MSCs have been clinically tested for the treatment of graft versus host diseases, virus-associated immune abnormalities, and chronic injuries in human immunodeficiency virus, hepatitis B virus, and influenza virus⁵⁴. MSC infusion has shown variable yet promising results in ARDS with viral or nonviral etiology through paracrine mechanisms including secretion of growth factors and cytokines as well as the release of EVs comprising exosomes and microvesicles. The mass spectroscopy-based analysis has revealed that the EV cargo contains more than 850 unique gene products and more than 150 miRNAs that modulate immune responses as illustrated [18-19].

MSC derived EVs infusion in Covid patients

The use of cell therapy, especially MSCs, to treat cancers and COVID-19 appears promising based on the observations and findings in published studies. MSC therapy has shown promise to suppress cytokine storms, prevent the over activation of the immune system, and repair the lung injury caused by SARS-CoV-2 infection. Cell-based therapy could be considered an alternative treatment to containing the public health crisis, such as outbreaks in hospitals and care units and the collapse of medical infrastructure. Additionally, vaccines are already reducing the overall COVID-19 cases in many countries. However, cell-based therapy could also be used to treat the long-term sequel e caused by SARS-CoV-2 infection in patients, especially those related to chronic inflammation [20, 21]. To recapitulate the symptoms and drug response of COVID-19 and cancer patients in vitro, SARS-CoV-2

studies using physiologically relevant human embryonic stem/induced pluripotent stem cell-derived somatic cells and organoids are ongoing. They are being used to investigate SARS-CoV-2 cell tropism, to develop COVID-19 therapeutic agents, and to examine the relationship between COVID-19 aggravation and human genetic backgrounds [22]. Acute respiratory distress syndrome in COVID and cancer patients is caused by a cytokine storm. Umbilical cord mesenchymal stromal cell (UC-MSC) influence proinflammatory Th2 cells to shift to an anti-inflammatory agent. An UC-MSC infusion was given for the experimental group, and normal saline for the control group. Our result showed 2.5 times significantly higher survival rate in the experimental group that achieved by modulating the immune system toward anti-inflammatory state [23].

Potential mechanism of MSC action in COVID-19 infected patients

SARS-CoV-2 enters cells through receptor-mediated endocytosis via interactions with cell surface protein angiotensin-converting enzyme II (ACE2) receptor with the assistance of transmembrane protease serine 2 (TMPRSS2) protease, thus triggering a complex immune response involved in T cells, dendritic cells, natural killer cells and macrophages. Engineering MSCs with immunomodulatory molecules enhance the efficacy of homing to damaged tissues or cells and attenuate the cytokine storm, ultimately improving patients' outcome [24]. Mesenchymal stem cells (MSC) derived from adult sources express high levels of ACE2, which could facilitate the SARS-Cov2 entry, compared with MSC derived from embryonic or pluripotent stem cell (iPSC)-derived MSC [25]. The latter population could be the most adequate sources for cell therapy of severe COVID-19 infection, as they could be less prone to SARS-Cov2 entry. SARS-CoV-2 enters into host cells through ACE2 and TMPRSS2. Mesenchymal stromal cells (MSCs) derived from amnios (A), cord blood (CB), cord tissue (CT), adipose tissue (AT) and bone marrow (BM) do not express these proteins, as demonstrated by RT-qPCR, western blot, ELISA and immunofluorescence. They are not infected by either spike pseudovirus, or by SARS-CoV-2 wild strain [25]. The recent clinical trials and the therapeutic benefits of mesenchymal stem cells in coronavirus-induced acute respiratory distress syndrome are critically reviewed. Then, the new advances in the field of tissue engineering relevant to the coronavirus infections, including three-dimensional models, to study disease progression or test the antiviral agents are described. Moreover, the potential applications of biomaterials for vaccine technology, and drug delivery are highlighted [25].

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SARS-CoV-2 wild strain [26]. The therapeutic potential of mesenchymal stem cells in acute respiratory distress syndrome-developed COVID-19 cases was tested in recently approved clinical trials. They possess several features facilitating the resorption of the alveolar exudate by type I and type II alveolar cells and improving the pulmonary microenvironment, thus recovering the lung functions in COVID-19 [27].

MSC therapy for immune/inflammatory pulmonary disorders

Broad immunomodulatory properties of human MSCs and MSC-derived products allow for therapeutic use in noninfectious—including chronic obstructive pulmonary disease, asthma, and idiopathic pulmonary fibrosis—and a number of infectious immune/inflammatory lung disorders [28]. In ARDS, pro-inflammatory cytokines contribute to the disruption of the alveolar – capillary membrane, edema, and pneumocyte damage. MSCs modulate the inflammatory milieu by T-cell and macrophage redirection, and anti-inflammatory cytokine production. Clinical trials assessing MSC therapy in ARDS have shown that MSCs have been associated with a favorable trend in mortality reduction, pulmonary function improvement, and cytokine correction [29]. Similar to two other lethal coronaviruses, SARS-CoV and MERS-CoV, SARS-CoV-2 induces excessive and aberrant host immune responses that are always accompanied by cytokine storms (CS) and subsequent ALI or even ARDS, resulting in multiple organ failure and death.2 Even in patients who were treated in intensive care units for CS, persistent inflammation led to serious sequelae of lung fibrosis, causing lung dysfunction and reduced quality of life.3 Although corticosteroid given to reverse catabolism in critical illness decreased the mortality after SARS and MERS infection, the clinical application of corticosteroid has been restricted in COVID-19, considering its delay in virus clearance and complications in survivors. There is an urgent need for advancing therapeutic interventions with both functions for CS suppression and lung reparation in critical patients [30, 31]. MSCs have been found to be capable of modulating immune responses, thereby reducing inflammation as well as immunopathology and protecting alveolar epithelial cells during ALI and ARDS.4-7 More importantly, MSCs were efficacious in reducing the nonproductive inflammation and in promoting lung generation in a phase 2 clinical trial (NCT03608592), as well as in patients with ALI and ARDS in clinical practice. 8-10 As a result, MSCs may alleviate the SARS-CoV-2-derived CS and ARDS, and have a potential effect on the treatment of subsequent chronic respiratory dysfunction and lung fibrosis [30]. To alleviate acute respiratory disease and reverse pulmonary fibrosis in intensive-care SARS-CoV-2-infected patients, three curative properties of MSCs have emerged: (a) directly inducing the apoptosis of activated T cells to relieve the aberrant and excessive immune responses, (b) homing toward specific injuries of lung to maintain homeostasis as well as promote regeneration, and (c) releasing cytokines to diminish inflammation and extracellular vesicles (EVs)

to stimulate tissue reparation.¹ Notably, it has been proved that MSC-released cytokines can potently inhibit neutrophil intravasation and enhance the differentiation of macrophages. ^{5, 6} Moreover, these MSC-released EVs can deliver microRNA, mRNA, DNA, proteins, and metabolites into host cells in specific injuries of the lung to promote lung repair as well as regeneration and restore lung function [32].

As the continuing epidemic threat of SARS-CoV-2 to global health and the fast-growing number of fatalities, advancing new therapeutic development becomes central or primary to minimize the death and sequelae from SARS-CoV-2 infection. Thus, MSCs should be considered as a potential treatment for these critical patients [33].

Mesenchymal stem cell therapy for COVID-19

Stem cell therapy proved to be very useful in treating a number of diseases including cancer, and diabetes. Mesenchymal stem cells (MSC) are characterized by low invasive nature and high proliferation rate, and additionally devoid of ethical & social issues that makes it as the preferred therapeutic option over others [34]. MSCs play an important role in immunomodulatory effects via secreting many types of cytokines by paracrine secretion or make direct interactions with immune cells. The source of MSCs can be peripheral blood (PB), bone marrow (BM), adipose tissues [(AT), buccal fat pad, abdominal fat, & infrapatellar fat pad], placenta, umbilical cord, Warton jelly, amniotic fluid, and blood cord. Therefore, it seems MSCs-based therapy may possibly be an ideal candidate for clinical trials or at least the combination of treatment to treat COVID-19 patients [34]. While we wait for a vaccine to come into the picture, convalescent plasma therapy, and repurposing the drugs treatment options proved to be suitable (if not perfect). We need to have suitable vaccine development, neutralizing nAbs antibody as prophylactic and therapeutic, and mesenchymal stem cell-based treatment options for effectively dealing with COVID-19. Until an ideal treatment comes, people must follow proper caution such as wearing masks, follow social distancing, and as much as possible do activities, which could be afforded through online mode/route [35].

Highlights

- Direct cytopathic effect and immunopathological pathogenesis are two of the main underlying mechanisms for severe pulmonary injury in patients with coronavirus and other viral disease

- Repurposed antiviral agents are among the most promising therapeutics for overcoming them

- Immunomodulatory effects of mesenchymal stem/stromal cells have potential to prevent the immune-mediated consequences of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

- Nucleic-acid-based approaches have gained much attention for treating patients with virus like COVID

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