Mesenchymal Stem Cells to Battle COVID-19

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What is a Mesenchymal Stem Cell? What Can it Do?

Mesenchymal stem cells (MSCs) are multipotent stem/progenitor cells that are present in different tissues, including the umbilical cord, bone marrow, and fat tissue. MSCs can self-renew by dividing and differentiate into cells of bone, cartilage, muscle and fat cells, and connective tissue. They are also famous for their ability to produce useful growth factors and cytokines. MSCs secrete multiple factors, including prostaglandin E2, interleukin-10, interleukin-1 receptor antagonist, interleukin (IL)-6, leukocyte inhibitory factor, nitric oxide, TNFα stimulated gene 6 (TSG-6), and many others, which limit immune response. In addition, MSCs skew maturing immune cell populations, i.e. populations of regulatory and anti-inflammatory T cells and dendritic cells become more abundant, while pro-inflammatory T cells, dendritic cells, and natural killers (NKs) decrease in numbers.

Due to these unique features, MSCs are considered a promising approach to treat autoimmune diseases and to manage the rejection of grafts. For over 10 years, they have been successfully used in the therapy of autoimmune diseases (rheumatoid arthritis, ulcerative colitis, type 1 diabetes, multiple sclerosis) and for the inhibition of transplanted organs rejection.

Mesenchymal Stem Cells and COVID-19. Rationale and Intentions

Now MSCs have a new “battlefield” – COVID-19. Severe COVID-19 is thought to result from hyperinflammation (overactive immune response) triggering cytokine storm and a prothrombotic state. A cytokine storm (or hypercytokinemia) is an uncontrolled and excessive release of cytokines, which are pro-inflammatory signaling molecules. A prothrombotic state (also called thrombophilia or hypercoagulability) is abnormal blood coagulation that increases the risk of thrombosis (blood clots in blood vessels).

Therefore, there is an urgent need for novel therapies that can alleviate the excessive inflammatory response associated with the cytokine storm and thrombosis. This has made researchers and clinical physicians test if MSC infusions can become such a novel therapy. MSCs are invulnerable to the virus SARS-CoV-2 because they lack the angiotensin-converting enzyme 2 (ACE2) receptor that SARS-CoV-2 uses for entry into cells. It is hypothesized that MSCs, due to their immunomodulatory abilities, can attenuate COVID-19 symptoms.

“We welcome the opportunity to …explore future development of our IMS001 product (investigational MSC product) in COVID-19 and ARDS from other causes,” commented Richard Kim, M.D., Chief Medical Officer of ImStem Biotechnology.

The COVID-19 pandemic has boosted not only scientific research and clinical practice but also made some commercial enterprises revise things of value. The Indian stem cell enterprise ReeLabs has offered to supply the patented stem cell product for FREE to all patients infected by COVID-19 in the country even after completion of the study. Given that India has a population of 1.4 billion, this IS a major commitment. “The sheer magnitude of the COVID-19 pandemic has sent shock waves throughout the world due to which ReeLabs has immediately recalibrated its priorities…,” stated Dr. Abhijit Bopardikar MD, Director ReeLabs.

MSCs and COVID-19. Achievements. Anti-inflammatory Effects and Clinical Observations. The first successful case of overcoming COVID-19 was reported for a 65-year-old woman in an intensive care unit of Baoshan Clinic (Kunming, the capital of Yunnan, China), who on day 3 after a MSC infusion started walking. A bunch of clinical trials of MSC therapies in COVID-19 patients have been launched. As early as of September 30, 2020, 44 studies involving the use of MSCs for the management of COVID-19 were registered in www.ClinicalTrials.gov database. By December 2020, this number had doubled. The results were quite impressive. For example, Lanzoni G. et al (2021) reported that 31 days after the first infusion, patient survival was 10 of 11 (91%) in the MSC group vs 5 of 12 (42%) in the control group (vehicle solution); serious adverse event (SAE)-free survival was significantly improved in the MSC group compared with the control group (SAEs affected two vs eight patients in the MSC and control group, respectively); and the time to recovery was significantly shorter in the MSC group compared with the control group. Analysis of pro-inflammatory cytokines in plasma demonstrated that their concentrations markedly and statistically significant decreased from day 0 to day 6 only in the MSC group. In parallel, an increase in anti-inflammatory cytokines such as IL-4, IL-5, and IL-10 was observed. In other trials, outcomes were also encouraging: lymphopenia (lymphocyte count), fever, shortness of breath, respiratory rate, and pneumonia infiltration and pulmonary lesions in radiological images, and oxygenation index were significantly recovered in patients, who received MSC therapy.

MSCs and COVID-19. Prospects. Regeneration and Repair. The regenerative potential of MSCs can also be beneficial in patients with severe COPVID-19 and its complications. MSCs contribute to tissue regeneration and repair as they are able to reduce an abnormal immune response, to differentiate into the target tissues and to secrete factors inducing host reparative and regenerative mechanisms. This includes stimulation of anti-scarring pathways and neovascularization. In respiratory diseases, not only the elimination of virus but also the repair of damaged lung tissues and are required. Acute respiratory

distress syndrome (ARDS) (including COVID-19 ARDS) is characterized by disruption of the alveolar-capillary membrane barrier, edema, hyperplasia, and pneumocystis. Pulmonary fibrosis is one of the most severe and serious sequela to ARDS. Hence, it is necessary not only inhibit the hyperinflammation but also stimulate the regeneration of damaged alveolar epithelial cells. MSCs were proven to have the potential of differentiating into the lung cells. The beneficial effects of MSCs in ARDS models and in clinical trials have been shown previously. MSCs secrete growth factors such as angiopoietin-1, epidermal growth factor (EGF), vascular endothelial growth factor A (VEGFA) and others that can promote repair of epithelial and endothelial cells. MSCs' derived factors have shown beneficial effects in pulmonary fibrosis in an acute lung injury model. Basing on the above, S. Sadeghi et al. (2020) believe that regenerative properties of MSCs could be used to treat COVID-19 patients.

However, the pulmonary tissue is not the only one that needs repairing. This coronavirus can cross the brain-blood barrier. Pathologic examination of the brain revealed necrosis of neurons and gliosis (proliferation or hypertrophy of glial cells in response to damage to the CNS). Stem cell transplantation was shown to ameliorate the increased meningitis-induced brain cell death and reactive gliosis in rats (Ahn SY et al. 2018). The use of MSCs reduced neuronal cell loss from the hippocampus and cortical neuronal and glial defects in traumatic brain injury rats (Chuang TJ et al. 2012). However, today there is no available information on completed or ongoing clinical trials of MSCs designed to assess their effects on CNS manifestations of COVID-19 or even on preclinical trials in animal models. Some companies, like the Indian research-oriented company Advancells and American company BrainStorm Cell Therapeutics, have experience in stem cell treatment of neurodegenerative disorders and could contribute to the developments of cell-based anti-COVID-19 therapies.

MSCs and COVID-19. Prospects. Can Stem Cells Be Used for COVID-19 Vaccination?

Cellular vaccine strategies have been mostly used against cancer. Cellular vaccines benefit from the direct transfer of transfected host cells for in vivo production of vaccine antigens. MSCs are a newfound platform for designing genetically engineered cellular vaccines because they can be efficient and safe vehicles for enhancing the host immune response. engineered cells enable us to deliver payloads in ways never before thought possible, enabling therapies to treat previously intractable common and rare diseases. Founded in 2016, BlueRock Therapeutics, has proven that engineered cells enable delivering “payloads in ways never before thought possible, enabling therapies to treat previously intractable common and rare diseases.” Using human-engineered MSCs to produce the SARS-CoV-2 N-protein antigen is one of the promising strategies that has been reported in a recent paper of Chinese researchers as a candidate for producing the COVID-19 vaccine. They showed that MSCs engineered to produce COVID-19 proteins could provide a new basis for effective vaccine development. Transfected

allergenic MSCs (carrying plasmids for SARS-CoV-2 N-protein) were injected in mice. Twenty days after vaccination, blood samples from the mice were tested for antibodies against N-protein. One dose of such vaccine led to antibody accumulation in the sera of injected mice.

One should admit that molecular mechanisms of MSCs' action are still not fully understood. Multidisciplinary and vigorous efforts are required to ensure that MSC intervention reaches its full potential.

- Advancells
- BlueRock Therapeutics
- BrainStorm Cell Therapeutics
- Imstem Biotechnology
- Reelabs