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Stem Cell–Based Therapy for Coronavirus Disease 2019

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The novel coronavirus disease 2019 (COVID-19) has grown to be a global public-health emergency since patients were first detected in Wuhan, China, in December 2019. As of April 9, 2020, the novel coronavirus (named as SARS-CoV-2 by the International Committee on Taxonomy of Viruses on February 11) has infected 83,251 and 1,484,811 patients in China and the world, respectively. However, we have neither confirmed effective antiviral medications nor vaccines available to deal with this emergency. In this commentary, we offer an alternative promising therapy for COVID-19, that is, mesenchymal stem cell transplantation.

Keywords: COVID-19, transplantation, clinical trial

The novel coronavirus disease 2019 (COVID-19) has grown to be a global public-health emergency since patients were first detected in Wuhan, China, in December 2019. As of April 9, 2020, the novel coronavirus (named as SARS-CoV-2 by the International Committee on Taxonomy of Viruses on February 11) has infected 83,251 and 1,484,811 patients in China and the world, respectively. However, we have neither confirmed effective antiviral medications nor vaccines available to deal with this emergency. Once infected, the patient mainly relies on his immune system to resist SARS-CoV-2, with supportive treatment given if complications occur.

Presently, many reports have summarized the clinical features of patients infected with COVID-19, revealing that most (>80%) of the patients had lymphopenia, and more than half of the ICU patients had higher plasma levels of granulocyte colony stimulating factor and tumor necrosis factor alpha (TNF-α), which exerted a cytokine storm, leading to acute respiratory distress syndrome [1–3]. Current available clinical interventions include respiratory support (mechanical ventilation, noninvasive ventilation, or invasive ventilation), antipyretic and nonspecifically antiviral medicine, corticosteroid, immunoregulation, and Traditional Chinese Medicine, among others [2–5]. Global mortality is reported to be 4.7% but varies widely by location between a reported low of 0.7% in Germany and a high of 10.8% in Italy [6]. Meanwhile, scientists have confirmed that the first step in the SARS-CoV-2 pathogenesis is the virus specifically recognizing the angiotensin I converting enzyme 2 receptor (ACE2) by its spike protein [7–9].

We have conducted basic research and clinical trials on mesenchymal stem cells (MSCs) for >20 years [10]. One previous study showed that MSCs could induce mature dendritic cells into a novel Jagged-2 dependent regulatory dendritic cell (DC) population, published in *Blood* [11]. Regulatory DCs (regDCs) play an important role in controlling immune homeostasis and can possess an immunosuppressive ability to induce specific immune tolerance and dampen Th2 type inflammation. We also reported that MSCs could decrease the differentiation of classical DCs from human CD34+ cells while increasing the differentiation of regDC, published in the *Journal of Immunology* [12,13]. Furthermore, interleukin-10 (IL-10) plays an essential role in maintaining the immunomodulatory property of regDC. All these interactions with different dendritic cells lead to a shift of the immune system from Th1 toward Th2 responses.

Based on those results, we believe that $ACE2^-$ MSCs could be beneficial for patients with COVID-19. We therefore conducted a clinical trial pilot study [14]. The results showed positive effects. MSCs played their immune modulation roles to reverse the lymphocyte subsets. A group of $CD14^+CD11c^+CD11b^{mid}$ regulatory DC cell population dramatically increased. Meanwhile, the level of TNF-α decreased significantly, and IL-10 increased in the MSC treatment group compared to the placebo control group. Furthermore, the gene expression profile showed that MSCs were $ACE2^-$ and $TMPRSS2^-$, suggesting the MSCs were free from COVID-19 infection [8]. Thus, the intravenous transplantation of MSCs was safe and effective for treatment in patients with COVID-19 pneumonia, especially for patients whose condition was critically severe.

In our study, human umbilical cord–derived MSCs (UC-MSCs) were used for transplantation. The cell product has been certified by the National Institutes for Food and Drug Control of China (authorization number: 2004L04792, 2006L01037, CXSB1900004). Umbilical cords were obtained from two healthy donors after normal deliveries of 38- to 40-week gestation with informed consent. UC-MSCs were isolated and cultured under Good Manufacturing

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Practice (GMP) conditions. Briefly, after removal of blood vessels, the mesenchymal tissue was cut into small fragments and centrifuged at 250 *g* for 5 min at room temperature. The resultant pellets were washed with serum-free Dulbecco's modified Eagle's medium (DMEM). Next, the cells were treated with 2 mg/mL collagenase type I solution for 4 h at 37°C, washed, and treated with 0.25% trypsin for 30 min at 37°C with agitation. Finally, the cells were washed and cultured in DMEM/F-12 supplemented with 2% fetal bovine serum (Gibco, Grand Island, NY), specific culture medium with a number of growth factors, 100 IU/mL penicillin and 100 μg/mL streptomycin. Cells were maintained at 37°C in a humidified incubator with 5% CO_2. Surface markers of UC-MSCs detected by flow cytometric should be positive (>95%) for CD90, CD105, and CD73 and negative for CD45, CD34, CD31, and HLA-DR. Quality control for the MSC included identity, purity, and safety, and differentiation potency evaluations were conducted following culture of the MSCs. The cells of passage 6 were used for transplantation.

Under this special emergency, Chinese researchers and clinicians are working together day and night to conduct a number of clinical trials [15]. As of April 9, 2020, 24 clinical trials of the registered 583 are being conducted with MSC therapy for COVID-19 (www.chictr.org.cn/index.aspx). But in China, the stem cell clinical trials are under the strict supervision of the National Health Commission of China or the National Institutes for Food and Drug Control of China. Of the 24 clinical trials, only five have received approval. Meanwhile, the National Stem Cell Therapy Commission for COVID-19 also supervises those stem-cell clinical trials. They have proposed an evaluation system of Regulation-Science-Cells-Progress-Quality (RSCPQ) to meet the challenge. Elsewhere, scientists from Brazil, Jordan, and France are also conducting MSC therapy clinical trials for COVID-19 (NCT04315987, NCT04313322, and NCT04333368, respectively). We hope these efforts combined with candid assessment and regulatory approval will soon provide an effective therapeutic intervention.

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Author Disclosure Statement

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