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Editorial

Mesenchymal Stem Cells in Treating Severe COVID-19

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Friedenstein., *et al*. first reported in the 1970s that locally applied culture-expanded populations of bone marrow stromal-derived fibroblastic cells remained at their injection sites under the renal capsule, where an ectopic hematopoiesis was begun. Later, mesenchymal stem (stromal) cells (MSCs) was described by Arnold Caplan's group as multipotent mesenchymal cell populations that can differentiate into several tissue types. MSC populations can be obtained from several non-bone marrow tissues, including umbilical cord, placenta, amniotic fluid, peripheral blood, and adipose tissue. By the year 2000, clinicians and investigators had increasingly become interested in intravenously applied MSCs. The concept began from the observation in children with osteogenesis imperfecta, an inherited enzyme deficiency of collagen synthesis by mesenchymal cells in bone that bone marrow transplantation can provide stromal cells able to synthesize intact collagen type I. Then, the conclusion was made that transplantation of isolated healthy allogeneic MSCs might cure the disease. Since then, the field for intravenous use of MSCs was opened.

After the year 2000, the intravenous administration of MSCs for therapeutic use was explored by a number of animal and human studies. These studies revealed that MSCs distribute to a variety of tissues after intravenous administration. MSCs are detectable at low or very low frequencies after transplantation. The signals from the injected MSCs were identified early after intravenous administration of the MSCs at the highest frequencies (80% of injected MSCs) in the lungs (capillary bed), followed by the liver and spleen, respectively, both in animals and humans. The MSCs accumulation in lung reduced from approximately 35% early after transplantation to 2% or less by day 10, while spleen had the highest signals by day 10 after transplantation, both in animals and humans.

The MSC signal (an *Alu* sequence DNA marker) fell exponentially, with a half-life of approximately 24 hours and complete practically disappearance after 4 days of MSCs injection. A previous study *in vitro* system revealed that murine MSCs inhibited functionality of the interstitial dendritic cells (DCs) through TLR-4-mediated signals in co-culture with monocytes. This study also demonstrated that human MSCs revealed a unique immunophenotype of alternatively activated human monocytes that were CD206-high, IL-6-high, IL-10-high, IL-12-low and TNF-α-low.

The immune suppressive effects of MSCs depend on the induction of the production of prostaglandin E2, or induction of indoleamine 2,3-dioxygenase, as a principal effector to inflammation. Indirectly, these data support the hypothesis of direct interaction between MSCs and antigen-presenting cells and/or monocytic cells *in vivo*. These studies strongly demonstrate the existence of interaction between cells of the immune system and transplanted MSCs. Exosomes, small membrane vesicles (40 - 100 nm in diameter) of endosomal origin derived from MScs have been identified to accumulate in the target cells of MSC therapy. Patients with severe graft-versus-host disease revealed marked improvement after the exosome infusion. The question for the biodistribution of MSCs is whether exosomes are formed by intravasally administration of MSCs.

Currently, during the COVID-19 pandemic, several trials on COVID-19 pneumonia or severe COVID-19 are underwent in China, such as ClinicalTrials.gov Identifier: NCT04252118, NCT04273646, NCT04276987, NCT04293692, NCT04302519, NCT04288102, etc. A recent

study by Zhao., *et al*. published in the journal "Aging and Disease" demonstrated that MSC therapy for 14 days could be effective in treating COVID-19 pneumonia. The pulmonary function and clinical symptoms of all patients with COVID-19 pneumonia in this study were significantly improved two days after MSC transplantation. Two moderate and one severe patients in this study were recovered and discharged in 10 days after therapy. MSCs can reduce the overproduction of immune cells caused by a reaction to the COVID-19 and reduce excessive levels of inflammatory cytokines and chemokines, thus regulating the immune system to the normal status, particularly in the elderly patients.

In conclusion, a number of questions of injected MSCs therapy include which contacts are made between MSCs and other cells in the blood circulation and are there physiological clearance pathways for transplanted MSCs. It is too early to compare the MSC-transplantation- therapy effectiveness and safety with other treatment modalities in treating COVID-19 pneumonia. More studies are needed to evaluate MSC-transplantation-therapy effectiveness and safety. Its most effectiveness therapy may be a combination of different treatment approaches.

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