Editorial

Stem cells and covid-19

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There has been extensive research into the regeneration of tissues and organs, and the restoration of damage done to them, with the use of stem cells.

Primordial stem cells are cells that are found in multicellular organisms. They are characterized by two basic qualities: the ability to divide and create similar cells as well as the ability to split and generate cells that are more specialized. That is, they possess the ability to generate multicellular subtypes, according to the cellular microenvironment. Depending on their source of origin, stem cells can be distinguished as ***embryonic*** or ***adult*** stem cells[1]. ***Embryonic*** stem cells are pluripotent cells which are derived from the inner mass of a blastocyst.

Adult stem cells refer to each type of cell in the body, which are characterized by the properties of self-regeneration and differentiation. Another term used for them is "*somatic*" and they can be found in both children and adults. ***Adult*** stem cells are located in many tissues playing a vital role in tissue development, maintenance and reparation[2]. They are characterized by high plasticity, or, in other words, high differentiation capacity. Adult stem cells of mesenchymal origin have been isolated from a variety of sources, including the **umbilical cord**, **bone marrow** and, most recently, the **adipose tissue**, and they have been used not only for aesthetic purposes, but also for the treatment of numerous incurable chronic diseases, such as Parkinson's disease, type 2 diabetes, congenital heart disease, inflammatory enteropathy, osteoarthritis and chronic kidney disease[1-10].

A significant number of clinical surveys have been published regarding the safety and effectiveness of mesenchymal stem cells used in the treatment of many chronic and acute diseases and they have had many promising results. Specifically, one study concerned their impact on incurable diseases of the respiratory system, such as idiopathic pulmonary fibrosis. In this study, mesenchymal stem cells were obtained by aspiration from adipose tissue[3,4].

As a result, it was certain that there would be references to the use of stem cells in research attempts to combat COVID-19 infections. One of the researchers' aims is to treat the most serious complications resulting from a COVID-19 infection,viral pneumonia and ARDS.

Clinical studies have shown the tropism of this virus for *alveolar type 2 cells and capillary epithelium* due to the high expression of **ACE2 receptors** in their cellular membranes, which allow the pathogen to enter[11]. As a result of the impact of the virus, the so-called **cytokine storm** is activated, a consequence of the proliferation and interaction of immune cells, with

macrophage as the main cell agent. **Cytokines** (IL-2, IL-6, IL-7, INFγ, GSCF, IP10, MCP1, MIP1A, TNFa) promote ***inflammation***, cause parenchymal damage with apoptosis and phagocytosis and irreversible lung tissue ***fibrosis***, which clinically manifests as pulmonary edema, gas exchange disorder, **ARDS** and acute heart failure, with a high mortality rate[12].

A vast number of surveys regarding the treatment of COVID-19 respiratory infection have commenced globally using **mesenchymal stem cells (MSCs), MSC derived conditioned media** (a complex of products that MSC-sproduce)**, extracellular vesicles (EVs)** (particles that are surrounded by a cellular membrane and that contain proteins, lipids, metabolites, as well as organelles of the cell itself), and a few other cell populations[13].

Scientists are looking into tackling the cataract of ***inflammation***, the binding of ***ACE2***, the utilization of ***EVs*** as a "means of transport" for antiviral drugs or other particles (RNA or proteins) and the ***regeneration*** of diseased tissues.

As a source of MSC, researchers used the following tissues: bone marrow, peripheral blood, adipose tissue (abdominal fat, infrapatellar fat pad, buccal fat pad) and embryonic tissue (placenta, umbilical cord, Warton's jelly, amniotic fluid, fetal liver).

MSCs are activated with the binding of pathogen molecules (viral RNA) to the specific receptors on their cell surface, releasing a variety of **mediators** (anti-inflammatory cytokines (like TGFβ, HGF, LIF, VEGF, EGF, BDNF and NGF), antimicrobial peptides, angiogenic growth factors and EVs. With this mechanism, mesenchymal stem cells (MSCs) present **immunomodulatory** and **regenerative** properties[7], as well as immediate **antiviral** activity, therefore they have the ability to mitigate the excessive immune response of the organism and prevent its devastating effects[14,15].

There is evidence that most of the therapeutic properties of MSCs are due to the production of **EVs**[10]. Hence, new therapeutic approaches may be developed. The benefits of this method are: controlled extracorporeal production of EVs, the feasible use of EVs as a "means of transport" for antiviral drugs or other particles (RNA or proteins) for target therapy and the avoidance of systematic use, given that EVs can be inhaled directly into the airways through the nose or via inhalation. Moreover, EVs, "adorned" with spike proteins of the pathogen, bind ACE2 receptors to compete with the virus for cellular uptake[16].

Leukemia inhibitory factor **(LIF)**- cytokine, which promotes cell growth and differentiation, and which belongs to the IL-6 group, plays an important role in the regeneration of damaged tissues, as well as in dealing with cytokine storm. It is produced by activated MSCs, yet with the aid of nanotechnology, **synthetic stem cells** (LIFNano), which can produce 1000 times the volume of LIF, this method reduces the cost of treatment[17,18].

It is significant to understand the rationale and existing data that support and negate effectiveness of MSCs in COVID-19 and respiratory virus infections in general, as well as to delineate the targeted patient population and potential cell therapy approaches[19]. Currently, there is an increasing number of clinical investigations of stem cell therapy methodologies for COVID-19, using a range of different cell sources, doses, dosing strategies and targeted patient populations. It is unfavorably important to understand the suggested mechanisms of MSC actions in this patient population[19].

In conclusion, in these difficult times, during the COVID pandemic, humanity needs to find an effective and safe treatment. Studies and clinical trials on treatments based on stem cells and their by products have begun all over the world[19-22], and the first results are optimistic, but they are nowhere near the final stage. In addition, it is noted that the trials must provide more information regarding the effectiveness and safety of this innovative and promising treatment.

CONFLICT OF INTEREST

None.

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