Stem Cell Reviews and Reports (2021) 17:291–292
https://doi.org/10.1007/s12015-020-10028-3

LETTER TO EDITOR

Epidermal Neural Crest Stem Cells as a Perspective for COVID-19 Treatment

Mohammad Saied Salehi[1] · Sareh Pandamooz[2] · Benjamin Jurek[3]

Published online: 19 August 2020

Currently, the world is facing a new challenge due to the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the coronavirus disease 2019 (COVID-19) pandemic. The SARS-CoV-2 hijacks and enters the cells via angiotensin I converting enzyme 2 receptor (ACE2). The ACE2 is expressed on linings of the arteries and veins throughout the body, but it is particularly dense on the cell lining of the alveoli, in particular alveolar type II cells, which renders them the most vulnerable cells to be infected. Based on the available evidence, it seems that many COVID-19 symptoms are not necessarily caused by the SARS-CoV-2 directly, but rather by a cytokine storm of tumor necrosis factor-alpha (TNFα) and interleukin (IL)-2, 6, 7. In combination with a hyperinflammation as a result of the infection-triggered host immune response might lead to the multiple organ dysfunction syndrome [1].

At present, several therapeutic approaches such as antiviral or anti-inflammatory drugs are used to medicate COVID-19 patients. Those treatment regimens had been developed to treat SARS-CoV as well as Middle East Respiratory Syndrome Coronavirus (MERS). Beside the pharmacological treatments, stem cell-based therapy has been considered as one of the possible strategies to revert the cytokine storm, to modulate the immune response and inflammation in order to treat COVID-19. Based on the World Health Organization International Clinical Trials Registry Platform, more than 60 clinical trials from countries like China, United States, Egypt, France, Iran, Turkey Spain and Jordan employed different types of stem cells to treat COVID-19.

Up until now, mesenchymal stem cells (MSCs) from sources like wharton's jelly/umbilical cord, adipose tissue, bone marrow, dental pulp, and menstrual blood is the most promising treatment option in the above-mentioned clinical trials. For instance, Leng and colleagues [2] reported that allogenic MSCs could improve the functional outcomes of seven COVID-19 patients, along with decreased serum levels of TNF-α, and increased IL-10 and VEGF compared to the placebo control group. In addition, RNA-sequence analysis in the transplanted MSCs revealed high mRNA levels of important trophic factors such as NGF, BDNF, EGF, VEGF, FGF, HGF, TGF-β and HGF.

Although some progress in MSC therapy for COVID-19 patients has been achieved, the main setback is that potential beneficial effects are highly context dependent, and a lack of convincing evidence that MSCs reduce the 28-day mortality [3, 4]. Given the mixed initial results derived from MSCs, we suggest to consider other types of stem cells that are accessible for autologous transplantation, have strong immunomodulatory potential to alleviate the cytokine storm, but without the drawbacks and context-dependency of the MSCs.

Epidermal neural crest stem cells (EPI-NCSCs) originate from the embryonic neural crest, located in the bulge of adult hair follicles. This type of stem cells display a high degree of plasticity, show absence of tumorigenicity, and can be well-differentiated into all neural crest derivatives [5]. They are abundant and can be isolated with a minimally invasive procedure. In addition, unlike bone marrow MSCs whose proliferation/differentiation potential dramatically declines with age, EPI-NCSCs isolated from elderlies preserved their multipotency in vivo and in vitro [6].

In cerebral ischemia, EPI-NCSCs and BM-MSCs show equal therapeutic potential [7]. In animal models of peripheral nerve injury [8] and stroke [7], EPI-NCSCs showed superior

This article belongs to the Topical Collection: *Special Issue on COVID-19 Pandemic and Stem Cells*
Guest Editor: Mariusz Z. Ratajczak

✉ Mohammad Saied Salehi
ms_salehi@sbu.ac.ir; saied_salehi@sums.ac.ir

[1] Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[2] Stem Cells Technology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[3] Department of Molecular and Cellular Anatomy, University of Regensburg, Regensburg, Germany

immunomodulation properties. Furthermore, EPI-NCSCs demonstrated their curative abilities in Alzheimer's disease, and in vivo as well as ex vivo models of spinal cord injury.

EPI-NCSCs are characterized by the expression of a variety of growth factors, including VEGF, FGF, TGF, IGF, NGF, BDNF, NT-3, and GDNF [9], all of which are essential for vascularization and cell survival. It has been previously reported that pre-treatment of stem cells with pharmacological agents, or using tunable materials as an artificial niche, can improve the expansion and/or differentiation of stem cells into mature cell types with enhanced therapeutic effects and tissue repair capabilities [10]. Similarly, the growth factor expression profile of EPI-NCSCs can be modulated by pharmacological drugs, and the stiffness of their substrate directs the fate of EPI-NCSCs differentiation [11].

In summary, we suggest a potential for the use of EPI-NSCSs in the fight against COVID-19, due to their multipotency, abundancy, accessibility, immunomodulatory properties, and rich trophic factor expression profile.

References

1. Blanco-Melo, D., Nilsson-Payant, B. E., Liu, W.-C., Uhl, S., Hoagland, D., Møller, R., Jordan, T. X., Oishi, K., Panis, M., Sachs, D., Wang, T. T., Schwartz, R. E., Lim, J. K., Albrecht, R. A., & tenOever, B. R. (2020). Imbalanced host response to sars-cov-2 drives development of covid-19. *Cell, 181*(5), 1036–1045.
2. Leng, Z., Zhu, R., Hou, W., Feng, Y., Yang, Y., Han, Q., Shan, G., Meng, F., du, D., Wang, S., Fan, J., Wang, W., Deng, L., Shi, H., Li, H., Hu, Z., Zhang, F., Gao, J., Liu, H., Li, X., Zhao, Y., Yin, K., He, X., Gao, Z., Wang, Y., Yang, B., Jin, R., Stambler, I., Lim, L. W., Su, H., Moskalev, A., Cano, A., Chakrabarti, S., Min, K. J., Ellison-Hughes, G., Caruso, C., Jin, K., & Zhao, R. C. (2020). Transplantation of ace2-mesenchymal stem cells improves the outcome of patients with covid-19 pneumonia. *Aging and Disease, 11*(2), 216–228.
3. Golchin, A., Seyedjafari, E., & Ardeshirylajimi, A. (2020). Mesenchymal stem cell therapy for covid-19: Present or future. *Stem Cell Reviews and Reports, 16*, 427–433.
4. Xiao, K., Hou, F., Huang, X., Li, B., Qian, Z. R., & Xie, L. (2020). Mesenchymal stem cells: Current clinical progress in ards and covid-19. *Stem Cell Research & Therapy, 11*(1), 1–7.
5. Sieber-Blum, M. (2010). Epidermal neural crest stem cells and their use in mouse models of spinal cord injury. *Brain Research Bulletin, 83*(5), 189–193.
6. Boroujeni, S. M., Koontz, A., Tseropoulos, G., Kerosuo, L., Mehrotra, P., Bajpai, V. K., et al. (2019). Neural crest stem cells from human epidermis of aged donors maintain their multipotency in vitro and in vivo. *Scientific Reports, 9*(1), 1–12.
7. Salehi, M. S., Pandamooz, S., Safari, A., Jurek, B., Tamadon, A., Namavar, M. R., Dianatpour, M., Dargahi, L., Azarpira, N., Fattahi, S., Shid Moosavi, S. M., Keshavarz, S., Khodabandeh, Z., Zare, S., Nazari, S., Heidari, M., Izadi, S., Poursadeghfard, M., & Borhani-Haghighi, A. (2020). Epidermal neural crest stem cell transplantation as a promising therapeutic strategy for ischemic stroke. *CNS Neuroscience & Therapeutics, 26*, 670–681.
8. Li, Y., Yao, D., Zhang, J., Liu, B., Zhang, L., Feng, H., & Li, B. (2017). The effects of epidermal neural crest stem cells on local inflammation microenvironment in the defected sciatic nerve of rats. *Frontiers in Molecular Neuroscience, 10*, 133.
9. Hu, Y. F., Gourab, K., Wells, C., Clewes, O., Schmit, B. D., & Sieber-Blum, M. (2010). Epidermal neural crest stem cell (epi-ncsc)—Mediated recovery of sensory function in a mouse model of spinal cord injury. *Stem Cell Reviews and Reports, 6*(2), 186–198.
10. Chrzanowski, W., Kim, S. Y., & McClements, L. (2020). Can stem cells beat covid-19: Advancing stem cells and extracellular vesicles toward mainstream medicine for lung injuries associated with sars-cov-2 infections. *Frontiers in Bioengineering and Biotechnology, 8*, 554.
11. Pandamooz, S., Jafari, A., Salehi, M. S., Jurek, B., Ahmadiani, A., Safari, A., Hassanajili, S., Borhani-Haghighi, A., Dianatpour, M., Niknejad, H., Azarpira, N., & Dargahi, L. (2020) Substrate stiffness affects the morphology and gene expression of epidermal neural crest stem cells in a short term culture. *Biotechnology and Bioengineering, 117*(2), 305–317.