



Dimethyl Fumarate Can Enhance the Potential Therapeutic Effects of Epidermal Neural Crest Stem Cells in COVID-19 Patients

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Dear editor,

We found Salehi et al.'s letter [1] very interesting. They proposed to investigate the potential therapeutic effects of epidermal neural crest stem cells (EPI-NCSCs) in covid-19 disease. There are ongoing trials investigating the efficacy of mesenchymal stem cells (MSCs) in treatment of COVID-19. Salehi et al. believed that EPI-NCSCs might be superior to MSCs due to their high proliferation ability, multi-lineage potential, and lower risk of carcinogenicity. EPI-NCSCs are potent sources of growth factors including fibroblast growth factor (FGF), Transforming growth factor (TGF), Insulin-like growth factor 1 (IGF), Vascular endothelial growth factor (VEGF), Brain derived neurotrophic factors (BDNF), Neurotrophin-3 (NT-3), Nerve growth factor (NGF) and glial cell-derived neurotrophic factor (GDNF). The results of a very recent clinical trial which investigated the therapeutic effects of mesenchymal stem cells (MSCs) in covid-19 patients showed the overexpression of major growth factors in transplanted MSCs [2].

Salehi et al. very briefly described, the beneficial effects of the combination of stem cells and pharmacologic agents in various diseases. This writing is a complementary letter on the potential therapeutic benefits of Dimethyl fumarate (DMF) and EPI-NCSCs combination therapy in covid-19 infection.

Dimethyl fumarate (DMF) and its dynamic metabolite mono methyl fumarate (MMF) have been firstly introduced as a treatment of psoriasis. Its clinical application was then

extended to cure relapsing remitting Multiple Sclerosis (RRMS). Its anti-inflammatory and anti-oxidants effects, particularly through activating nuclear factor erythroid-derived 2(E2)-related factor (Nrf-2) have been reported [3]. Suppressing nuclear translocation of nuclear factor- κ B (NF- κ B) and enhancing the expression of hydroxyl carboxylic acid receptor (HCAR) were also introduced as the other main mechanisms of action. Regulation of NF- κ B activity was reported to be effective in treating Covid-19 infection [4]. The vast anti-inflammatory effects of HCAR in various organs were also reported [5].

DMF, was recently proposed as a potential therapeutic option for Covid-19 patients. Its potential benefits in reducing alveolar cell injury were explained thoroughly with a focus on its Nrf-2 activating mechanisms of action [6]. Virus entry and replication were also explained to be negatively affected by DMF. Activating secretory leukocyte protease inhibitor (SLPI) as an anti-protease and inhibiting transmembrane protease serine 2 (TMPRSS2) as a protease protein were the main mechanisms introduced. Enhancing the expression of anti-viral genes retinoic acid-inducible gene-I (RIG-I) and Interferon beta (IFN- β) were presented as the other potential benefits of DMF therapy in covid-19 patients [6]. DMF and MMF also exert a huge immunomodulatory effects through regulating a wide range of immune cells that determine the host innate and acquired immune response. DMF can effectively change the T- helper cells profile from type 1 to type 2. Not only B and T cells but also macrophages, dendritic and natural killer cells are affected [6]. The final result of these vast regulatory effects can be the inhibition of cytokine storm which is known as the main triggered factor for the disease severity in covid-19 patients. The results of a new case series recommended the continuation of DMF therapy in younger MS patients with normal lymphocyte count who become infected with COVID-19 in their course of therapy [7]. Other researchers also confirmed the safety of starting DMF treatment in healthy young or pediatric MS patients [7].

Combination of stem cell therapy with pharmacologic agents have been vastly investigated in a wide range of disease

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models. Our recent investigation demonstrated that DMF effectively induced the over expression of EPI-NCSCs trophic factors profile, particularly those with neurotrophic effects [8]. The enhanced trophic factor profile of MSCs applied in treatment of covid-19 patients [2] can be assumed as a potential therapeutic effect of stem cells in this infection.

According to above-mentioned findings, it can be assumed that DMF-treated EPI-NCSCs may have even more beneficial effects in treatment of SARS-Cov-2 infection than EPI-NCSCs. Considering the previous reports on the beneficial effects of both EPI-NCSCs [9] and DMF [10] in neurological disorders, DMF- treated EPI-NCSCs may possess the greater advantages in neurological complications of SARS-Cov-2 infection.

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