Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Medical Hypotheses 142 (2020) 109769

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Letter to Editors

Mesenchymal stem cell (MSc) secretome: A possible therapeutic strategy for intensive-care COVID-19 patients

ARTICLE INFO

Keywords:
MSc secretome
COVID-19
Novel strategy

ABSTRACT

As an emerging global health challenge, COVID-19 requires international knowledge to reach novel possible therapeutic strategies, especially for intensive-care patients. During the early stages of infection, pneumocytes II are the primary infected cells, harming the respiratory system. We have previous evidence in murine models that MSc's secretome can be used to treat pulmonary injuries induced with bleomycin, due to its content: growth factors, extracellular vesicles, and exosomes. We hypothesize and strongly recommend MSc secretome testing and production, in *xenofree* conditions, to be used as an alternative approach in SARS-Cov-2 patients in critical conditions.

Introduction

The World Health Organization (WHO) has recently recognized severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak as a global health concern [1]. The severe acute respiratory syndrome (SARS) caused by COVID represents a global public health threat, as shown by the high contamination rates in China, and now Europe, the new pandemic epicenter [2]. Witnessing a health system's collapse with the lack of trained personal and specific equipment for COVID-19 treatment and control, it is evident that this issue is not about another "regular flu", as repeatedly claimed during the early stages of the outbreak.

COVID-19 respiratory syndrome physiopathology is not yet totally elucidated, although recent research indicated a possible resemblance with SARS-CoV, a similar virus that causes acute inflammation, which might be related to the viral replication machinery and cascade [3–6]. SARS-CoV-2 is the seventh virus in the *Coronaviradae* family with the capacity to infect humans, just as SARS-CoV and MERS-CoV. It is well known that, just like SARS-CoV, this new virus can invade human cells using the viral S spike protein which interacts with the angiotensin-converting enzyme II (ACE2). This interaction has ten times the molecular affinity observed in SARS-CoV and may explain the fast dissemination rates observed worldwide [12,13]. Besides that, Pöhlmann's research group has shown that the TMPRSS2 molecule has an important role during infection, and strategies targeting its inhibition might be a way to hinder virus entry. During the early stages of infection, type II pneumocytes are the primarily infected cell type. Nevertheless, other cell types can also be a target for SARS-CoV-2: bronchial cells, macrophages, monocytes, and enteric cells. Furthermore, studies in recent patients (2019–2020) reported a high interleukin six (IL-6) secretion or even the so-called "cytokine storm", promoting uncontrolled pulmonary inflation in elderly comorbidity-affected individuals as diabetes, hypertension, bronchial asthma, and cancer carriers [3,4].

São Paulo State University (UNESP) has conducted recent studies in partnership with the University of São Paulo (USP) in murine models, investigating novel therapeutic methods using adipose tissue-derived mesenchymal stem cells (Ad-MSC) and its secretome present at conditioned media (CM), to treat pulmonary injuries induced with bleomycin [7,8]. Under these experimental protocols, we have reported a significant injury reduction. Therefore, we propose that the CM produced by Ad-MSC cultivation, in *xenofree* conditions, could be an effective therapeutic alternative for patients with poor clinical recovery or those in need of intensive methods [3,8].

Moreover, we have enough scientific evidence that relates aging to the high prevalence of chronic degenerative diseases with increasing morbidity among the elderly [9]. It is well-known that aging is related to cell senescence, which compromises its proliferative potential and leads to the appearance of a specific secretory phenotype, which creates an unfavorable tissue microenvironment. In other words, the aged and unregulated Ad-MSC secretory phenotype contributes to tissue damage.

MSc's role in orchestrating development, tissue maintenance, and repair, mainly producing several growth factors is unquestionable. Besides its stem-cell potency, its therapeutic properties can also be attributed to the capacity of secreting multiple critical factors (hormones and cytokines) for tissue regeneration. Hence, the CM is usually rich in exosomes, extracellular vesicles (EV) and growth factors. Among different products, CM represents a complex mixture of Ad-MSC's secreted products, which is now considered a reasonable and alternative approach in cell therapy. In addition to the previous facts, van Asten's research group reported that the fibroblast growth factor (FGF), isolated in Ad-MSC secretome, exhibited viral replication inhibition properties [11]. The isolation and production of young EV might have an effective therapeutic potential in aging pulmonary injuries [10].

Finally, we hypothesize and strongly recommend the production of large amounts of Ad-MSC's conditioned media, in GMP and *xenofree* conditions, to be used as an alternative approach in SARS-Cov-2 patients in critical conditions, and as an additional method, to register cured patients to collect their hyperimmune plasma, which could also be used as treatment.

Disclosure statement

The author reports no conflict of interest according to ICMJE Form for Disclosure of Potential Conflicts of Interest

https://doi.org/10.1016/j.mehy.2020.109769
Received 27 March 2020; Accepted 21 April 2020

Author contribution

We declare that all author's contributions were equally needed for this construct, and that each author added relevant, up-to-date information.

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