Magna Scientia Uceva (2021) 1:1, 6-10
ISSN: 2805-6884 e-ISSN: 2805-6701
https://doi.org/10.54502/msuceva.v1n1a2

Reflection Research Article

Medicine

COVID-19: Impact in endothelial function and therapy with Mesenchymal Stromal Cells

La COVID-19: Impacto en la función endotelial y terapia con células estromales mesenquimales

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First draft submitted: 15-05-2021
Accepted for publication: 23-07-2021
Published online: 09-09-2021

Key words:

COVID-19 pathophysiology; endothelial disfunction; immune cells; mesenchymal stromal cells; pathogenesis.

Palabras clave:

Células estromales mesenquimales; células inmunes; disfunción endotelial; fisiopatología de la COVID-19; patogénesis.

Citation:

Longo de Freitas C, Okochi Alves da silva PY, Pinho Franco M do C, de Almeida DC. COVID-19: Impact in endothelial function and therapy with Mesenchymal Stromal Cells. Magna Scientia UCEVA 2021;1: 6-10. https://doi.org/10.54502/msuceva.v1n1a2.

Abstract

The new pandemic of SARS-CoV-2 Betacoronavirus, has spread worldwide, and infected millions of individuals causing the disease denominated of COVID-19. Further on flu symptoms, due to the high tropism of virus, has most been observed in the COVID-19 pathophysiology: acute heart failure, thromboembolism events, acute renal failure, neurological and liver damage, and multiple organ failure, with special attention to endothelial disfunction. Hence, elucidate whether virus target the endothelium is a crucial step to understand COVID-19 pathogenesis. However, the permissiveness of blood vessels during SARS-CoV-2 infection remains unclear, but regardless endothelial infection, the vascular disfunction may occurred in response to molecular inflammatory signaling triggered by immune cells that attempt to limit infection. Thus, alternative therapies using mesenchymal stromal cells (MSCs) can change this scenario and help critically ill patients. In this reflection, we attempt to discuss COVID-19 pathophysiology with impact in endothelial function and explore the applicability of MSC-based therapies as alternative treatment.

Resumen

La nueva pandemia de Betacoronavirus SARS-CoV-2, se ha extendido por todo el mundo y ha infectado a millones de personas, causando la enfermedad denominada COVID-19. Además de los síntomas de gripe, debido al alto tropismo del virus, se han observado principalmente en la fisiopatología de la COVID-19: insuficiencia cardíaca aguda, eventos de tromboembolismo, insuficiencia renal aguda, daño neurológico y hepático y falla multiorgánica, con especial atención a la disfunción endotelial. Por lo tanto, dilucidar si el virus se dirige al endotelio es un paso crucial para comprender la patogénesis de COVID-19. Sin embargo, la permisividad de los vasos sanguíneos durante la infección por SARS-CoV-2 sigue sin estar clara, pero independientemente de la infección endotelial, la disfunción vascular puede ocurrir en respuesta a la señalización inflamatoria molecular desencadenada por células inmunes que intentan limitar la infección. Por lo tanto, las terapias alternativas que utilizan células estromales mesenquimales (MSC) pueden cambiar este escenario y ayudar a los pacientes críticamente enfermos. En esta reflexión, intentamos discutir la fisiopatología de COVID-19 con impacto en la función endotelial y explorar la aplicabilidad de terapias basadas en MSC como tratamiento alternativo.

COVID-19 and Sars-Cov-2 pathophysiology

Currently, the world is facing the new pandemic of SARS-CoV-2 coronavirus, responsible for the COVID-19 disease. SARS-CoV-2 is a positive single-stranded RNA-virus belonging to subgroup of Betacoronavirus of the Coronaviridae family [1]. The disease is similar to the severe acute respiratory syndrome (SARS), which was the first coronavirus (SARS-CoV-1) epidemic in the world registered in southeastern China [2–4]. To date (September 2021) around 218.946.836 people, have been diagnosed worldwide with SARS-CoV-2 infection, with 4.539.723 deaths and 5. 289.724.918 vaccine doses distributed. Specifically, in the American continent, was confirmed 84.498.889 cases, with 2.043.623 deaths, according to data from the World Health Organization (WHO) [5].

The most common symptoms in mild to moderate cases of the disease are fever, dry cough, throat irritation, breathing difficulty, myalgia, nausea and/or vomiting, diarrhea, headache [6,7]; and more specifically, asnomy or augesia [8]. Additionally, critically ill patients also present profound lymphopenia, caused by SARS-CoV-2 infection [9–11].

Due to the high tropism of virus at tissues as heart, kidney and blood vessels has been observed in the pathophysiology of COVID-19: acute heart failure, dysrhythmia, myocarditis, thromboembolism events (arterial and venal) [7]; acute renal failure [12,13]; neurological damage such as impaired consciousness, stroke; liver dysfunction; blood dysfunction (i.e. metabolic acidosis) [6]; thrombosis [14]; septic shock and multiple organ failure [15,16].

In this context, to enter in host cell, the SARS-CoV-2 virus bind its surface protein (Spike S) with the angiotensin II converting enzyme (receptor ACE2), turning some subunits of its protein S editable by proteolytic enzyme as TMPRSS2, which cleaves protein S into S1, S2 and S2' counterparts promoting cellular infection [17,18]. Both ACE2 and TMPRSS2 receptors are widely distributed in alveolar cells, kidney, and also in many other organs, especially in the capillary endothelium [1].

The endothelium consists in a semi-permeable barrier between body fluids and tissues, comprising an extensive network for micro and macromolecules transportation including cells. Thus, elucidate whether virus target the endothelium in a direct way or as bystanders, is a crucial step to understand COVID-19 pathogenesis. The permissiveness of endothelial cells during SARS-CoV-2 infection is controversial and remains unclear. Fosse et al. [19], demonstrated that only human coronary artery endothelial cells (HCAECs) were infected by SARS-CoV-2 virus when compared to five other different endothelial cell lineages, however, did not promote virus replication. Conversely, Liu et al. [20], identified in lungs of both nonhuman primates and autopsied COVID-19 patients that SARS-CoV-2 directly infects mature vascular endothelial cells [20]. However, regardless endothelial infection, the vascular disfunction in COVID-19 patients may occurred as a result of molecular inflammatory signaling from infected cells or collateral tissue damage when immune cells attempt to limit infection.

This step initiates in the early stages of SARS-CoV-2 infection mainly at nasal epithelial cells, bronchial cells, and pneumocytes. When the virus reaches the alveolar lumen, it triggers an inflammatory response that promote the recruitment of immune cells such as neutrophils, monocytes, and T cells, which become infected [21,22]. In sequence, the virus overactive an inflammatory cascade in these immune cells accompanied by extensive release of molecules (i.e., IL-2, IL-6, IL-7, GSCF, IP-10, MCP1, MIP1A and TNF-α), which was widely known as *"cytokine storm"*, that attack principally surround tissues as lung and endothelium [10]. Hence, this immunological disorder, in severe cases, affects the tissue homeostasis leading to even more serious secondary complications such as multiorgan failure.

MSC homing and immunomodulation

Over the last decade, mesenchymal stromal cells (MSCs) have been the focus of many cell-based therapies to treat various type of disorders, including metabolic, degenerative, and inflammatory diseases, with focus in supporting tissue repair and regeneration of damaged tissues (see figure 1). MSCs have the ability to influence the tissue behavior (i.e., endothelial tissue), and vice-

versa. This crosstalk involves the selective migration ability of MSCs toward sites of injury, a phenomenon called *"homing"*. This homing process is promoted by specific chemokines and cytokines secreted by damage cells (EGF, IGF, PDGF, VEGF, SDF-1, TNF-α, IL-1, IL-6, IL-8, VCAM-1, MCP-1, MCP-3, and G-CSF), which are chemo-attractive and trigger MSCs mobilization (figure 1).

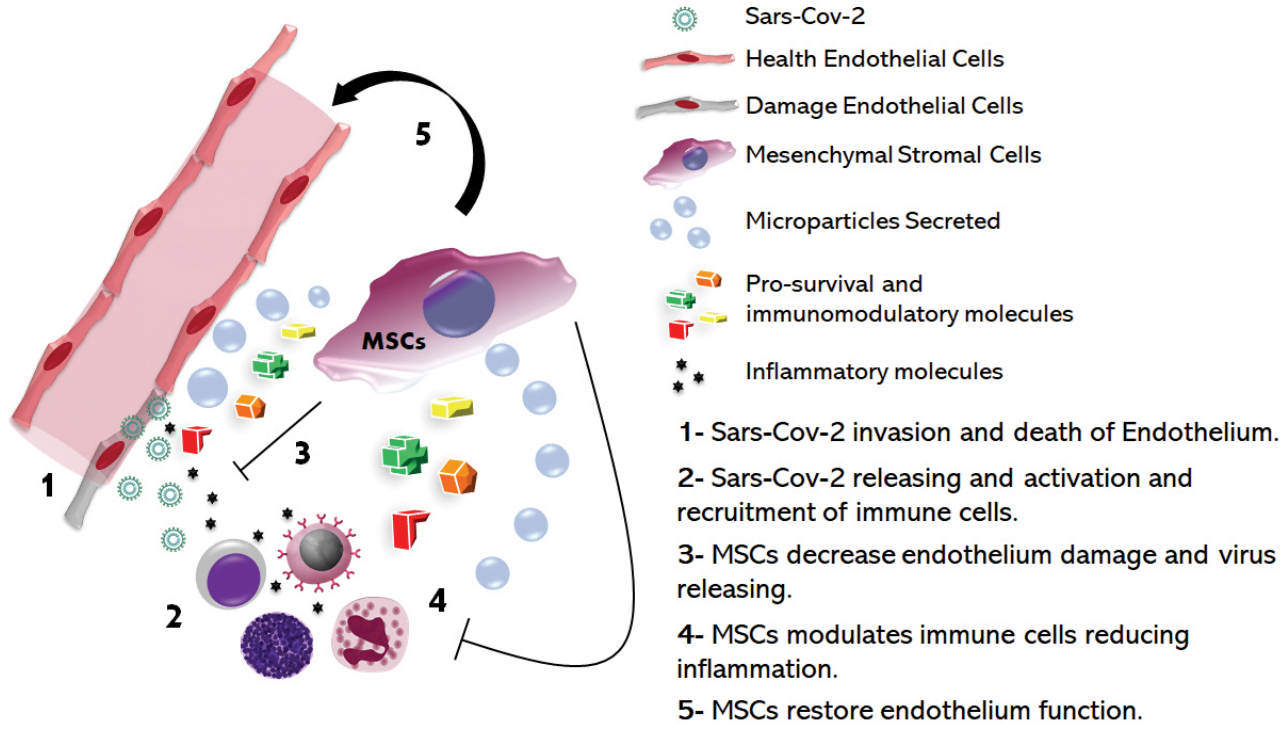

Figure 1. Mesenchymal Stromal Cells (MSC) possible action mechanism during endothelial inflammation mediated by Sars-Cov-2 infection
Sars-Cov-2 direct/indirectly causes damage to endothelial cells that release *"death signals"* to immune cells. After stimulated, the immune cells turn activated and secrets pro-inflammatory molecules intensifying endothelial injury and disfunction. By secretion of pro-survival and immunomodulatory molecules, the Mesenchymal Stromal Cells can decrease endothelium damage and viral infection, beyond modulates immune cells reducing inflammation and restoring tissue function.

At injury site, ligand-receptor interactions with adhesion molecules (selectins and integrins) are necessary for MSCs adhesion and rolling into injured tissues [23]. After tissue internalization, the MSCs alter the microenvironment through secretion of paracrine regulatory factors such as cytokines, chemokines and growth factors (IDO-1, PGE-2, iNOS, IL-6, TGF-β, HGF, and HLA-G5), that not only modulates cells but present angiogenic, anti-inflammatory, anti-fibrotic and immunosuppressive properties, modulating the function of immune cell (i.e., B and T lymphocytes, dendritic cells, natural killer cells, monocytes, neutrophils, and macrophages), and promoting tissue repair [24]. Taken together, these properties have led to the use of MSCs as an attractive and promising cell therapy in the context of acute respiratory distress syndrome (ARDS) seen in severe COVID-19 patients (figure 1).

MSC and COVID-19: perspectives and new insights

Clinical applications of MSCs have been registered at the National Institute of Health Clinical Trials [25] about COVID-19. In fact, there are 39 recruiting and ongoing

interventional trials studying MSCs to the treatment of ARDS, pneumonia, cytokine storm, pulmonary infection, SARS-Cov-2 induced pulmonary fibrosis and acute kidney injury, in the context of COVID-19 complications (September, 2021). These clinical trials involve MSCs derived from Wharton Jelly, adipose tissue, umbilical cord, placenta and human dental pulp and bone marrow as source of treatment or combined with other drugs such as oseltamivir, hormones, azithromycin, antibiotics, or hydroxychloroquine. Although, cell source, dosage and timing has not been stablished yet, these clinical studies are critical and can bring encouraging results, considering that phase I and II trials, have already demonstrated a partial effectiveness of MSCs treatment, where a reduction in inflammatory serologic markers and shorter-time period of hospitalization were observed [26].

In summary, MSC-based therapies can provide valuable information in the course of new treatment and new strategies to modulate endothelial function, and other tissues, specifically in the context of COVID-19.

Consent for publication

Authors read and approved the final manuscript.

Competing interests

Authors declares have no competing interests. This document only reflects the points of view of the authors and not those of their institutions.

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She is a doctoral student in the Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, Brazil (UNIFESP/ Brazil). Her research line is defined as "use of organ-on-chip to study the endothelium-kidney axis in SARS-CoV-2 infection; and therapeutic strategies with Mesenchymal Stem Cells.", graduated in Biomedicine at the University Center of Faculdades Metropolitanas Unidas (FMU/Brazil), completed in 2013. Areas of expertise: medicine, biological sciences, immunology and microbiology.

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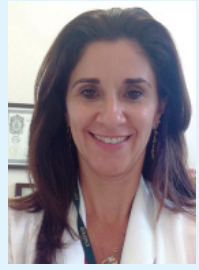

Studied Biomedicine and she started his research career at the department of pharmacology at the University of São Paulo where she also accomplished his doctoral thesis. In the following years she worked in the field of vascular biology with the focus on fetal programming. The main topics of her research group are fetal programming of cardiovascular diseases and exploration of novel targets involved in the development of cardiometabolic disease focusing on endothelial function as well as biomarker research.

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