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STEM CELLS IN THE TREATMENT OF COVID-19 ACUTE RESPIRATORY SYNDROME: What do we know so far?

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ABSTRACT

According Stem cells are nonspecific cellular systems, found in different regions of the human body, which are characterized by self-renewal and differentiation into other specialized cell types. Mesenchymal stem cells have angiogenic, anti-apoptotic, immunomodulatory, anti-oxidant and anti-inflammatory properties, mainly due to the release of paracrine factors, which has enabled their study in several health processes, including lung damage. Its attributes help in modulating the immune response, decreasing inflammation and contributing to the endogenous pulmonary repair of patients affected by the acute respiratory distress syndrome, a process that can be identified in patients severely affected by COVID-19. Finally, the present review article concludes that the use of mesenchymal stem cells can act by reducing the phenomenon of cytokine storm, showing itself as a promising option for the treatment of several lung diseases, resulting from exacerbated inflammation, including infection by the pandemic virus SARS-CoV-2.

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INTRODUCTION

COVID-19, an emerging disease caused by the SARS-CoV-2 virus, has already reached the mark of 31,798,308 confirmed cases and 973,653 deaths worldwide, according to reports from the World Health Organization (WHO) released on the 20th September 2020 (ECDC, 2020). The disease that gave rise to a pandemic is believed to have arisen in Wuhan, China in December 2019 when several health facilities reported cases of pneumonia of unknown cause (Zhu *et al.,* 2020). The mechanism of entry into cells by the virus depends on the binding of the Spike (S) protein to specific cellular receptors. The affinity with Angiotensin-Converting Enzyme (ACE2) receptors and Transmembrane Protease Serine 2 (TMPRSS2) are shown to be the main binding determinants for subsequent fusion of the virus membrane with that of human cells (Hoffmann *et al., 2020;* Wan *et al.,* 2020; Zhou *et al.,* 2020b). These receptors are expressed in several types of cells, with emphasis on the airway epithelial cells and type II alveolar of the pulmonary parenchyma (Sungnak *et al.*, 2020). Is largely, patients affected by the new coronavirus have an immunological capacity to eliminate the virus efficiently, making the disease asymptomatic (in 81.4% of cases) or presenting mild symptoms such as fever, cough and mild lung inflammation (Borges do Nascimento *et al.,* 2020; Harrell *et al.,* 2020). However, some patients may progress to overactivation of immune cells, with excessive release of inflammatory cytokines and chemokines, which can lead to the development of pulmonary edema, acute respiratory distress syndrome (ARDS) and even death - approximately 3% of people affected (Borges do Nascimento *et al.,* 2020; Vardhana; Wolchok, 2020). In this sense, the main challenge in the medical field has been to suppress the high mortality rate in individuals severely affected by the disease. The Stem Cells (SC) are cells present in the organism that have the ability to replicate, in addition to undergoing differentiation processes in several other cell types, being able to assume different functions, related to the tissue in which it specializes(Garcia; Roque; Silva, 2017). Mesenchymal stem cells (MSC) represent a subdivision of CS characterized by multipotency, which can give rise to mesenchymal cells from adult organs, in the presence of extracellular matrix and specific growth factors (Ambrosio *et al.,* 2020). Currently, therapies with MSCs have been used for a series of processes in the health area, which include oral rehabilitation (Garcia; Roque; Silva, 2017), cardiac regenerative therapy, neural diseases, liver failure, leukemia, among others (Volarevic *et al.,* 2011). In this range of applications, studies associated with pulmonary regeneration and immunomodulation in ARDS processes stand out (Walter; Ware; Matthay, 2014). In view of the need for effective therapy, much research has turned to the

development of new treatments for SARS-CoV-2 infection *(Mehta et al.,* 2020). This study consists of a literature review that sought to identify possible therapeutic actions of mesenchymal stem cells (MSCs) in pulmonary diseases and ARDS, highlighting a basis for clinical implications in the COVID-19 pandemic.

MATERIALS AND METHODS

The present study corresponded to an integrative literature review, carried out from March to December 2020. For this, articles were surveyed in the Google Scholar, SciELO and PUBMED databases. For the search for content on the bases described, the central theme was "*Mesenchymal stem cells*", with subdivisions, "*MSCs in Acute Respiratory Distress Syndrome*", "*MSCs in lung injury*" and "*Possible action of MSCs against COVID-19*". To complement the database searches, a manual search was also carried out on the references of the eligible studies. The articles were based on descriptors created by the Virtual Health Library developed (http://decs.bvs.br/ homepage. htm) from MeSH - Medical Subject Headings of the US National Library of Medicine (NLM), which allows the terminology common in Portuguese, English and Spanish. The descriptors were: Mesenchymal stem cells, COVID-19 and Acute Respiratory Distress Syndrome. The inclusion criteria for the articles selected for this research were: "*Articles published in journals indexed in the databases mentioned above*"; "*Articles published in Portuguese, English or Spanish*"; "*Articles published in the period from 2005 to 2020*". In this sense, no restrictions were applied to the sample of studies, and articles unrelated to the descriptors of the pre-established theme were excluded.

RESULTS AND DISCUSSION

Mesenchymal Stem Cells: The MSCs are cells found in the human body, which have the capacity for self-renewal, giving rise to identical cells, as well as the property of differentiating into other more mature cell types, such as blood, muscle, fat, bone, cartilage or other cells (Xiao *et al*., 2020). These cells can be isolated from adipose tissue, bone marrow, amniotic fluid, umbilical cord, placenta, menstrual blood and dental pulp, as shown in Figure 1, and it is believed that their main physiological role is related to replacement of injured tissues (Main; Munsie; O'Connor, 2014; Volarevic *et al.,* 2011). Another property of great clinical interest for MSC is related to its immunomodulatory and anti-inflammatory action (Walter; Ware; Matthay, 2014). Reports demonstrate the action of MSCs in halting the proliferation of immune T cells, as well as cytokine secretion and cytotoxicity, in addition to eliminating the activation of Natural Killer (NK) cells and other immunomodulatory actions (Gao *et al.,* 2016). For these characteristics, many studies have turned to its use as a therapeutic agent in the treatment of autoimmune or degenerative diseases (Volarevic *et al.,* 2011). One of the great advantages of MSCs is related to the reduced expression of type II major histocompatibility complex (MHC) antigens, which gives them the hypoimmunogenic characteristic, avoiding possible allogeneic rejections after grafting (Volarevic *et al.,* 2018). In addition, studies have found that the gene expression profile of MSCs is negative for ACE2 and TMPRSS2, indicating that such cells cannot be infected with SARS-CoV-2 (Leng *et al.,* 2020).

SARS-CoV-2 and treatments: Currently, there is no proven therapy against SARS-CoV-2 infection and the clinical management of patients affected by COVID-19 is mainly based on supportive therapy, treatment of symptoms and efforts to prevent the occurrence of respiratory failure (Pascarella *et al.,* 2020). In this scenario, it is essential to adopt practices that guarantee the isolation of infected individuals, as well as the limitation of social contact, between individuals, in a general social aspect, keeping hospital beds available for more serious cases of the disease (Singhal, 2020). Today, there are several studies underway to analyze existing drugs and their possible action against COVID-19, and considering the urgency of the need for such therapies, the World Health Organization (WHO) launched the clinical trial "*Solidarity*" that unites efforts from around the world

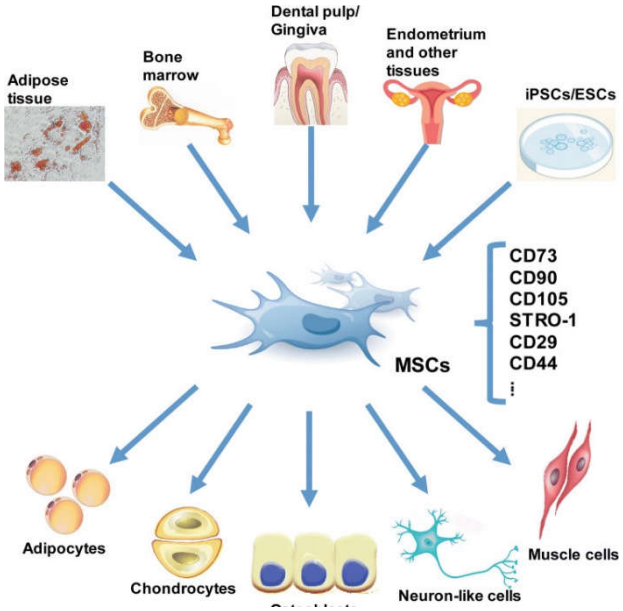

Figure 1. Illustrative representation of the ways of obtaining and transforming potentials of MSCs (Fan *et al.*, 2020).

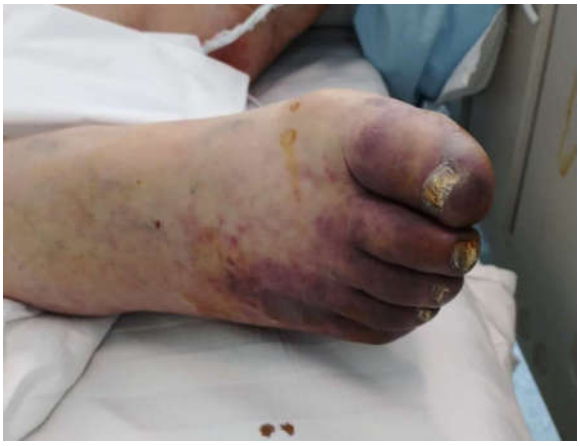

Figure 2. Ischemic changes of toes in one COVID-19 patient with severe type (Lin *et al.*, 2020).

to investigate the efficacy of drugs in the treatment of COVID-19, which has enabled the reduction of time spent on randomized clinical trials by up to 80% (Solidarity clinical trial for COVID-19 treatments , [s.d.]). The Solidarity trial involves the study of antiviral drugs such as Remdesivir, Lopinavir, Ritonavir, in addition to antimalarial agents such as Chloroquine and Hydroxychloroquine, drugs used in the treatment of multiple sclerosis, such as IFNβ-1ª and others, such as Baricitinib, Galidesivir, Ribavirin and Azithromycin (Jakhmola *et al.,* 2020). In addition, studies indicate the use of photodynamic therapy to promote cytotoxic effects and the possibility of its use in SARS-CoV-2 infection (Queiroz *et al.,* 2020). Anticoagulant-based therapy is indicated in cases of early-stage disease, in which the affected individuals have a D-dimer value four times higher than normal, in order to avoid overactivation of coagulation due to the inflammatory and infectious processes that can generate ischemic condition (Lin *et al.,* 2020), as seen in Figure 2. The use of glucocorticoids, such as dexamethasone, has also been the subject of research with an anti-inflammatory focus, aiming to modulate lung injury induced by inflammation (Asselah *et al*., 2021). Clinical trials demonstrate that patients hospitalized with COVID-19 who underwent oral or intravenous use of dexamethasone had a lower incidence of death compared with the usual treatment group, in patients who received invasive mechanical ventilation and those who received oxygen without mechanical ventilation invasive (Recovery, 2020). Another strategy, aimed at preventing infection, is vaccines, which make it possible to reduce disease morbidity and mortality more economically than treatment (Asselah et al., 2021). Several study groups and companies strive to develop vaccines against

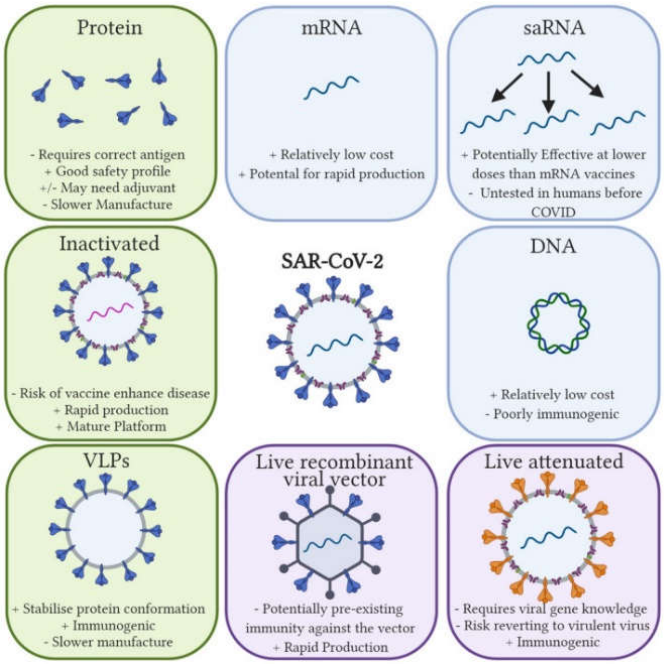

Figure 3. Vaccine platforms (Tregoning *et al.*, 2020).

COVID-19 using different strategies that can be subdivided into those based on proteins, inactivated viruses, vector vaccines, live attenuated virus and nucleic acid (Tregoning *et al.,* 2020), as it is observed, briefly, some characteristics in Figure 3.

MSCs in Acute Respiratory Distress Syndrome (ARDS): ARDS is a syndrome caused by inflammatory lesions of the alveolar-capillary membrane, causing an increase in pulmonary permeability, with fluid accumulation and edema in the air spaces (Bhatia; Zemans; Jeyaseelan, 2012). Clinically, alveolar rupture together with interstitial edema and the impregnation of inflammatory cells leads to clinical pictures of severe hypoxemia, which is associated with its high mortality rate, which is around 40% (Rubenfeld *et al.,* 2005). ARDS has a strong relationship with exacerbated inflammation and studies have shown the ability of MSCs to have an anti-inflammatory action, especially in the release of paracrine factors that have therapeutic potential for inflammatory diseases of the airways (Walter; Ware; Matthay, 2014). Studies also demonstrate the role of MSCs in protecting pulmonary epithelial cells exposed to pro-inflammatory cytokines, as well as their potential to induce pulmonary epithelial repair in mouses (Fan *et al.,* 2020; LI *et al.,* 2016; Main; Munsie; O'Connor, 2014). In addition to these actions, MSCs have angiogenic, anti-apoptotic and antioxidant properties that can be of great clinical interest (Fan *et al.,* 2020). The MSCs, in studies, have also shown action to prevent the proliferation of inflammatory cells that produce cytokines, such as IFN- γ and IL-17 CD4 + Th1 and Th17, as well as the expression of a programmed death ligand that induces apoptosis in effectors T cells, being able to decrease its concentration in the injured lung (Harrell *et al.,* 2020). In addition to suppressing the harmful immune response to lung tissues, MSC-based therapy has important angiomodulatory properties, and studies have demonstrated its action in improving oxygen supply in ischemic tissues, helping to regenerate them through the release of pro-angiogenic factors (Maacha *et al.,* 2020). Another possibility of using MSCs in the treatment of lung injuries is related to their possibility of differentiation, by means of grafting the injured tissue, helping in the structural and functional repair of the damage. However, studies show that the graft rate is not satisfactory in lung injury models, being restricted to less than 1%. For this reason, researchers have focused more on analyzing the immunomodulatory, anti-apoptotic and angiogenic factors of MSCs (Loi *et al.,* 2006; Rojas *et al.,* 2005; Xiao *et al.*, 2020). In summary, as shown in Figure 4, MSCs play an important role in the interaction with cells through mitochondrial transfer, epithelial and endothelial repair, bacterial and alveolar fluid clearance, in addition to exerting anti-inflammatory and

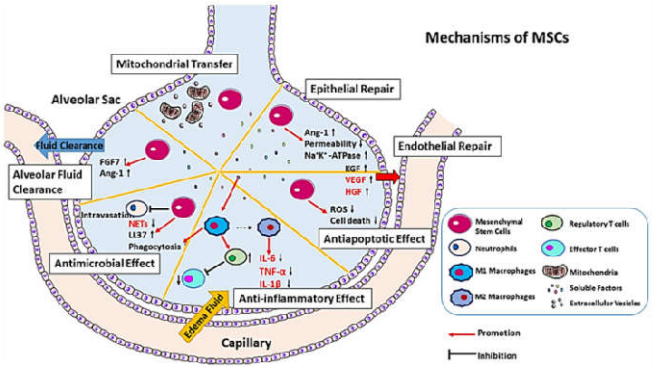

Figure 4. Schematic diagram of the mechanisms of action of MSCs in ARDS (Xiao *et al.*, 2020).

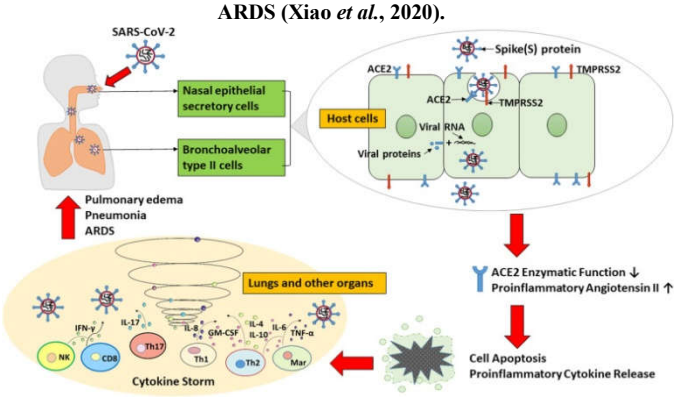

Figure 5. Schematic diagram of how SARS-CoV-2 causes COVID-19 (Xiao *et al.*, 2020).

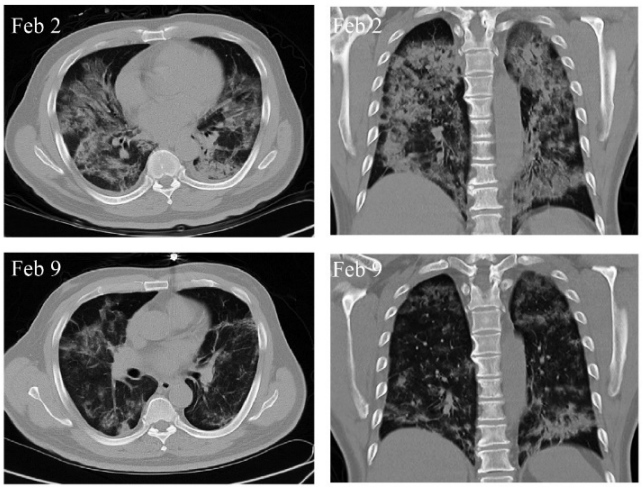

Figure 6. Computed tomography (CT) images of the chest of a patient with critically severe COVID-19 (adapted) (Leng *et al.*, 2020).

anti-apoptotic effects. These cells promote the differentiation of macrophages, increasing the activity of phagocytosis, as well as the production of anti-inflammatory cytokines, also inhibiting pro-inflammatory factors, which is beneficial for tissue repair and can prevent the release of a large amount of cytokines by the immune system(Xiao *et al.,* 2020).

Potential of MSCs at COVID-19: As mentioned, the SARS-CoV-2 virus has a great power of infection in type II alveolar epithelial cells (Sungnak *et al.,* 2020). These cells secrete chemokines capable of attracting immune cells and consequent production of a large number of pro-inflammatory cytokines, generating a phenomenon called cytokine storm, as shown schematically in Figure 5, which is the main cause of ARDS in affected patients by COVID-19 (Taghavi-Farahabadi *et al.,* 2020). Several cytokines have been identified in patients with COVID-19, involved in the cytokine storm that can give rise to inflammation-induced lung damage, leading to pneumonia, ARDS and even death (Taghavi-Farahabadi *et al.,* 2020; Zhou *et al.,* 2020). The ARDS in patients affected by COVID-19 may be accompanied by Disseminated Intravascular Coagulation (DIC), with

the potential to progress towards multiple organ failure, with this combination, ARDS and DIC, being the main cause of death in SARS-CoV-2 infected patients worldwide, featuring 13.9% of cases (Prete *et al.,* 2020). The marked increase in the inflammatory parameters that precedes ARDS are responsible for the marked edema in the alveolar wall and in the pulmonary interstices, which gives the disease a radiographic aspect of ground glass on computed tomography scans of the chest region (Prete *et al.,* 2020). In this sense, the main mechanism of interest for MSCs in the treatment of COVID-19 is related to its anti-inflammatory role, reducing the production of pro-inflammatory cytokines and decreasing the phenomenon of cytokine storm (Liu *et al.,* 2020). In addition, the release of keratinocyte growth factor (KGF) by MSCs can assist in the repair and proliferation of the alveolar epithelium (Shyamsundar *et al.,* 2014). In a clinical trial conducted in Youan, China, it was found that the use of MSCs (1×10^6 cells/kg), via systemic intravenous administration, in seven patients with COVID-19 supposedly improved the clinical status of all, in 14 days of study follow-up, without adverse effects, indicating that it is a safe and effective therapeutic technique (Leng *et al.,* 2020). The disappearance of cytokine-secreting immune cells was highlighted, as well as an easing of symptoms and improvement of lung function (Leng *et al.,* 2020). Such results can be seen in Figure 6, which shows a patient with COVID-19 undergoing treatment with MSCs on January 31, in which, on February 2, his lung was completely invaded by pneumonia, which showed a wide disappearance in the February 9th after treatment (Leng *et al.,* 2020).

Conclusion

In view of the review carried out, the literature highlights the potential and application of mesenchymal stem cells in several health processes. Several scientific studies indicate its ability to assist in the recovery of lung injuries, in cases of acute respiratory syndrome caused by SARS-CoV-2 infection, through the release of paracrine factors, as well as its angiogenic, anti-apoptotic, antioxidant and immunoregulatory capacity. Thus, according to the studies surveyed, MSC-based therapy can act by reducing the phenomenon called "cytokine storm, showing itself as a promising option in combating a variety of lung diseases, including COVID-19. However, despite research and studies being at an accelerated pace, systematic analyzes are necessary to evaluate the new clinical data reported, in order to prove its real effectiveness.

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