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Mesenchymal stem cells: a new perspective in the treatment of coronavirus-induced pneumonia (COVID-19)

Células-tronco mesenquimais: uma nova perspectiva no tratamento da pneumonia induzida pelo SARS-Cov-2 (COVID-19)

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ABSTRACT: The biology of stem cells is one of the most dynamic and promising fields in the biological sciences, as it is the basis for the development of organisms. Its biological complexity has demanded efforts from several lines of research aiming mainly at its therapeutic use. Mesenchymal stem cells (MSCs), after their infusion into the recipient organism, tend to accumulate in the lung, improving the microenvironment, protecting the epithelial cells of the alveoli and preventing the formation of fibrosis in order to restore the function of the lungs. Through safe and effective processes to suppress inflammatory processes and repair lung tissue, MSCs appear as a promising therapeutic approach for the treatment of respiratory diseases. In this work, we address the state of the art and the therapeutic potential of MSCs in the treatment of patients affected by pneumonia inCOVID-19.

Keywords: Coronavirus infections; Coronavirus; Mesenchymal stem cells; Pneumonia; Respiratory diseases.

RESUMO: A biologia das células-tronco é um dos campos mais dinâmicos e promissores das ciências biológicas, pois é a base do desenvolvimento dos organismos. Sua complexidade biológica vem demandando esforços de diversas linhas de pesquisa visando principalmente sua utilização terapêutica. As células-tronco mesenquimais (CTMs), após sua infusão no organismo receptor, tendem a se acumular no pulmão melhorando o microambiente, protegendo as células epiteliais dos alvéolos e prevenindo a formação de fibrose de forma a restaurar a função dos pulmões. Por meio dos processos seguros e eficazes de supressão dos processos inflamatórios e reparação do tecido pulmonar, as CTMs surgem como uma promissora abordagem terapêutica para o tratamento de doenças respiratórias. Neste trabalho abordamos o estado da arte e o potencial terapêutico das CTMs no tratamento de pacientes acometidos por pneumonia em decorrência da COVID-19.

Descritores: Infecções por coronavírus; Coronavírus; Células-tronco mesenquimais; Pneumonia; Doenças respiratórias.

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INTRODUCTION

Coronavirus (CoVs) is an important pathogen, usually associated with respiratory diseases and gastrointestinal infections, which affects both humans and animals. CoVs is a virus belonging to the *Coronaviridae* family which is composed of the genera *Alphacoronavirus*, *Betacoronavirus*, *Deltacoronavirus* and *Gammacorovavirus* as well as several subgenera and species. Having been reported in several animal species, including cattle, pigs, horses, felines, canines, rodents, camels, bats, civets, rabbits, among other animals and avian species. In humans, the coronavirus (HCoVs) was initially isolated by Tyrrell and Bynoe in 1965, from both adults and children, who had a respiratory infection, and were later classified as HCoV-229E (genus *Alphacoronavirus*) and HCoV-0c43 (genus *Betacoronavirus*)[1-3]. In the early 2000s, HCoV-NL63 (genus *Alphacoronavirus*) and HCoV-HKU1 strain A (genus *Betacoronavirus* - subgenus *Embecovirus)* were isolated from people affected by bronchitis and pneumonia respectively. In February 2003, in Guangdong province, southern China, a *Betacoronavirus* strain B (subgenus *Sarbecovirus*) derived from bats, with the civet as an intermediate host, was responsible for giving rise to a severe respiratory disease that was eventually called severe acute coronavirus-derived respiratory syndrome (SARS-CoV). This ended up resulting in an epidemic of 8098 cases, reported in 29 countries located in North America, South America, Europe and Asia, with 774 deaths (9.5% lethality rate)[4]. In 2005, in Hong Kong, two independent groups identified coronavirus similar to SARS-CoV with the bat as a natural host and possibly the civet as an intermediate host. Guangzhou markets, where live or slaughtered wild animals are traded, presented themselves as the possible dissemination focus of SARS-CoV, through the consumption of meat[5,6]. In 2012, a *Betacoronavirus* Lineage C (subgenus *Merbecovirus*), from camels and dromedaries, was responsible, in Saudi Arabia, for giving rise to the Middle East respiratory syndrome (MERS-CoV), very similar to SARS[7,8]. According to data from the World Health Organization, by the end of 2019, a total of 2494 cases were confirmed, resulting in 858 deaths (lethality rate of 34.4%)[9]. At the end of 2019, in the city of Wuhan, Hubei province, China, SARS-CoV-2 emerged, which has 88% of the genomic sequence identical to that of Betacoronavirus identified in bats, but differs by 79% from SARS-CoV[10] . In common, patients had a history of visiting the local seafood market near Huanan, a province south of Hubei, where it is suspected to be the origin of zoonotic transmission. The symptoms initially shown by those infected were those of common pneumonia - however, the patients progressed shortly thereafter to an acute respiratory distress syndrome. On January 7, 2020, the Center for Disease Control and Prevention in China confirmed the existence of a new coronavirus which was called SARS-CoV-2 which has been spreading worldwide, which led the World Health Organization to decree, in March 11, 2020, the pandemic picture.

Although humans can be affected by different coronaviruses, all have been shown to originate in animals. The coronaviruses SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-NL63 and HCoV-229E had their possible origin from the bat, while HCoV-OC43 and HCoV-HKU1 probably derived from rodents[11] (Table 1, Figure 1).

Table 1. Coronaviruses that infect humans

VIRUSES	GENDER	DISCOVERED	NATURAL HOST	INTERMEDIATE HOST	RECEPTOR
CoV-NL-63	*Alphacoronavirus*	1965	Bat	Unknown	Angiotensin-converting enzyme-2
CoV-229E	*Alphacoronavirus*	1967	Bat	Alpacas	Aminopeptidase N
SARS-CoV	*Betacoronavirus*	2003	Bat	Masked Palm Civet	Angiotensin-converting enzyme-2
CoV-OC43	*Betacoronavirus*	2004	Rodent	Cattle	9-0-Acetylsalicylic acid
CoV-HKU-1	*Betacoronavirus*	2005	Rodent	Unknown	9-0-Acetylsalicylic acid
MARS-CoV	*Betacoronavirus*	2012	Bat	Camel and Dromedary	Dipeptidyl Peptidase 4
SARS-CoV-2	*Betacoronavirus*	2019	Bat	Unknown	Angiotensin-converting enzyme-2

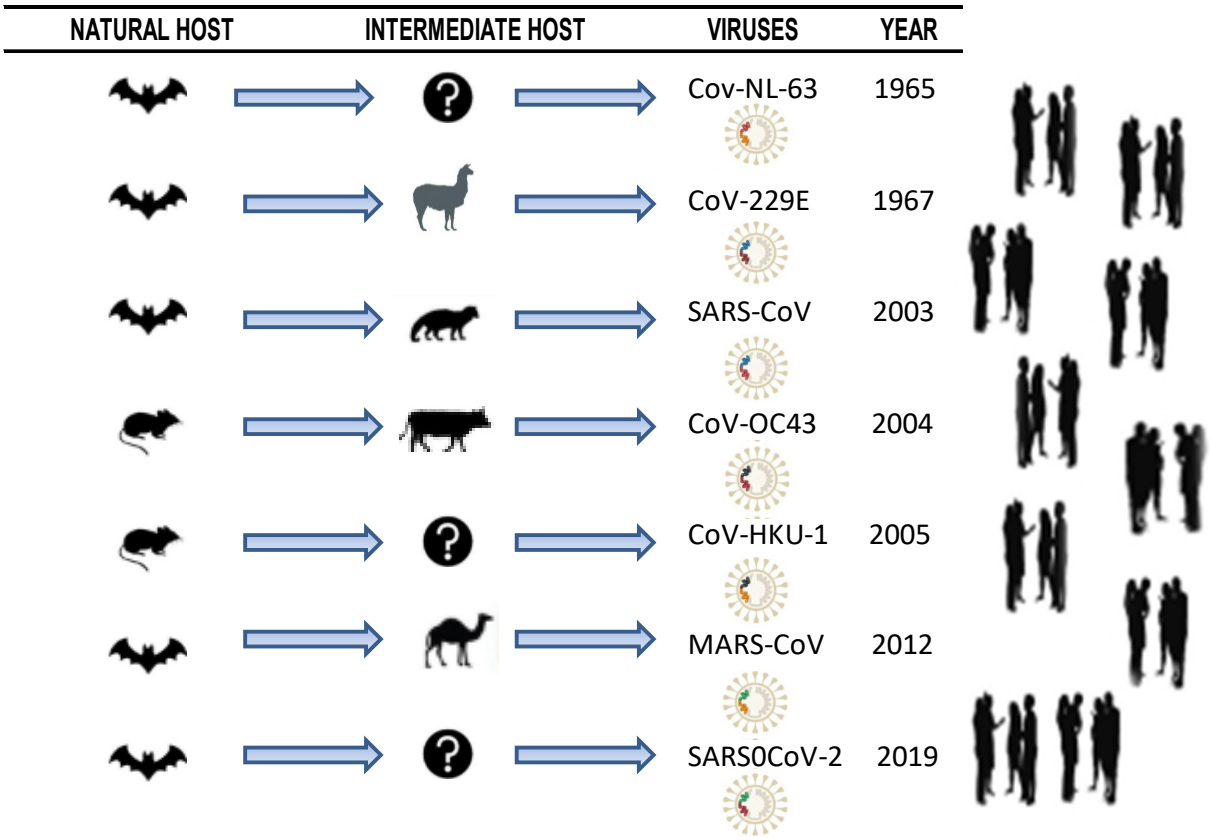

Figure 1. Evolution cycle of the subtypes of strains of the coronavirus over the years[11]

SARS-CoV-2 has its genome composed of a single strand of 29.9 kb RNA (the largest known viral RNA genome), positive sense, which interacts with nucleoprotein[12]. The SARS-CoV-2 genome has a variable number (6 to 11) of the open reading phase (ORFs), two thirds of which are located in the first ORF (ORF 1a / b) - which translates two polyproteins (ppla and pplab), in addition to encoding 16 non-structural proteins. The remaining ORFs encode accessory and structural proteins. The remainder of the genome encodes four structural proteins that make up CoVs and membrane proteins, envelope proteins, nucleocapsid protein, Spike surface glycoprotein and some ancillary proteins that interfere with the host's innate immune response[6] (Figure 2). The surface glycoprotein Spike plays a fundamental role in the SARS-CoV-2 infection process, as it is responsible for the recognition of the cell receptor, the angiotensin-converting enzyme 2 (ACE2), and is thus fundamental in the process of tropism to the host and the virus transmission capacity[13]. The Spike surface glycoprotein is functionally divided into two domains: S1 and S2 responsible, respectively, for the processes of binding to the ACE2 receptor and cell membrane fusion. The SARS-CoV-2 receptor-binding domain (RBD) is usually located in the C-terminal domain of S1. Due to the SARS-CoV-2 viral replication mechanism, it has a high frequency of recombination and a high mutation rate, in addition to the intra and interspecific transmission process, SARS-CoV-2 is capable of giving rise to new strains of coronavirus[3].

The infection caused by the coronavirus has an incubation period that can vary from 2 to 5 days. After the incubation period, infected patients tend to have symptoms such as high fever (temperature above 38.4ºC), headache and myalgia. About 10% to 20% of patients have diarrhea. The characteristic respiratory symptoms, such as dry cough, dyspnea and positive chest X-ray, develop several days after the onset of the disease, approximately one week. The most susceptible groups of individuals are those over 65 years of age and / or underlying diseases such as hypertension, diabetes, heart disease and respiratory diseases. Most patients affected by characteristic respiratory symptoms tend to develop pneumonia[10,14]. In more severe cases, patients may present with metabolic acidosis, septic shock, dysfunction in the blood coagulation process and multiple organ failure[15].

Although mesenchymal stem cells (MSCs) (Figure 2) have been known for some time, their biology and therapeutic action have, in recent decades, become an object of intense interest on the part of the scientific community. MSCs have emerged in the literature due to their high immunomodulatory and repairing potential which are applicable to the field of medicine. Currently, it is known

that all body tissues have their own MSC reservoir which is responsible for homeostasis in the tissue environment.

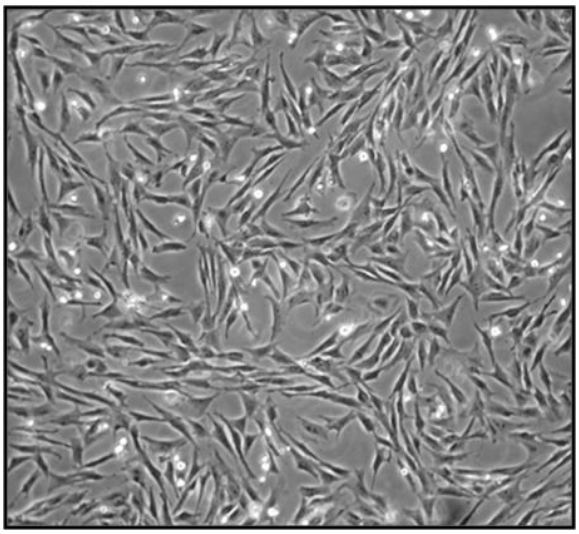

Figure 2. Fibroblastoid morphological aspect of mesenchymal stem cells

MSCs are characterized by being undifferentiated, spindle-shaped, long and flat cells, with fibroblastoid morphology, the ability to adhere to polymeric surfaces, high proliferation potential, the ability to differentiate into osteogenic strains, chondrogen and adipogenesis. In addition, more than 95% of cells must express surface markers CD105, CD73 and CD90 as well as less than 2% must express CD14, CD19, CD34, CD45 and HLA-DR. Due to their potential for in vitro expansion, the ability to treat tissue injuries, maintain their immunomodulatory and differentiation properties, even after long periods of cryopreservation, MSCs are a potential resource for both trials and clinical therapies. However, the ability of MSCs to self-renew for a limited time in vitro and their life span varies from species to species, is an important factor to consider when considering a therapeutic approach.

THERAPEUTIC PERSPECTIVE

The respiratory system is constantly exposed to several factors that tend to alter pulmonary homeostasis, which is maintained through the interaction between the alveolar and immunological epithelial cells present in the pulmonary microenvironment. Among the main symptoms identified in patients affected by the new coronavirus (SARS-CoV-2) we can mention: fever, dry cough, tiredness, loss of smell or taste, diarrhea, pain or discomfort, rash, discoloration of the fingers or fingers. feet and difficulty breathing. However, the main cause of death in patients with more severe infections is ARDS (Acute Respiratory Difficulty Syndrome). ARDS is a more severe spectrum of acute lung injury (ALI) composed of diffuse alveolar damage and non-cardiogenic pulmonary edema, clinically characterized by hypoxemic respiratory failure and the presence of bilateral pulmonary infiltrate, requiring the use of a mechanical ventilator[16]. In these cases the pathophysiology of SRDA is similar to severe community-acquired pneumonia caused by viruses and bacteria. Patients who develop the severe form of the disease may develop a cytokine shock syndrome in which there is overproduction of pro-inflammatory cytokines with early response, such as tumor necrosis factor (TNF-α), IL-6 and IL-1β characterizing a syndrome that promotes increased vascular hyperpermeability, multiple organ failure and eventually death[17].

Therefore, therapeutic solutions that are immunomodulatory or anticytokines become viable for the stabilization of the inflammatory process, such as the application of intravenous immunoglobulins and steroid use[18]. The lung injury repair process is modulated by a set of factors such as cell matrix metalloproteinases (MMPs), cytokines and growth factors produced by immune epithelial cells resident in the lung, fibroblasts and chondrocytes[19].

STEM CELL THERAPY

Stem cell therapy has been the target of intense basic, pre-clinical and clinical research, and its safety and efficacy have been proven[20,21]. The functional improvements have been attributed mainly to the immunomodulatory effects resulting from the secretion of paracrine factors by the MSCs, which has been helping to reduce the morbidity and mortality rates of various diseases. Due to their capacity to modulate the processes of proliferation, activation and functionality of cells of the immune system, MSCs appear as a promising therapeutic approach for acute or chronic lung diseases. In addition, the potential to differentiate into type II alveolar epithelial cells (EATII) is added, as evaluated in in vitro experiments[22,23].

After being infused into the patient, MSCs begin their paracrine action by secreting growth factors such as keratinocyte growth factor (KGF), vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) promoting the regeneration of epithelial cells, protection of vascular permeability and prevention of apoptosis of endothelial cells in order to promote the repair process of EATII cells. In addition, MSCs act to reduce the presence of neutrophils, suppress the production of pro-inflammatory cytokines IL-6 and TNF-α and stimulate the ability of alveolar macrophages to produce the anti-inflammatory factor IL-10[24-27].

In a pilot study carried out by Dr. Zhao's team, ten patients were selected, four men and six women aged between 45 and 75 years old, confirmed for HCoV-19 using the RT-PCR technique, affected by a picture pneumonia resulting from SARS-CoV-2 infection, seven of which

were submitted to a single intravenous administration of human MSCs at a concentration of 1x106 cells per kilogram of body weight and three used as placebo. Among the patients undergoing the infusion of MSCs, one had a critical condition, one had a severe condition and two had a non-severe condition. The three patients used as control, had a severe syndrome. Before the infusion of MSCs, patients had a low oxygen saturation, high fever (38.5 ℃ ± 0.5 ℃), shortness of breath, weakness, loss of appetite and pneumonia. In the study, the patients were followed for a period of 14 days and, after 2 to 4 days, a significant improvement in symptoms was observed in all patients submitted to the application of MSCs, without detecting adverse effects. Analysis of the chest images showed a significant reduction in chest infiltration. Laboratory results showed a significant decrease in the pro-inflammatory cytokine TNF-α and an increase in IL-10 levels, when compared to patients treated with conventional therapy. An increase in the rate of peripheral lymphocytes was observed with the phenotypic restoration of CD4 + and dendritic cells and a decrease in C-reactive protein. Most patients had negative results for SARS-CoV-2 nucleic acids, via RT-PCR, starting one week after the infusion of MSCs. The data also demonstrated an increase in gene expression of anti-inflammatory and trophic factors such as TGF-β, HGF, IL-10, LIF, GAL, NOA1, FGF, VEGF, EGF, BDNF and NGF in CTMs, proving the increase in their function modulator[28].

In China, a case study was carried out of a 65-year-old patient who, despite the intensive therapy she was undergoing, remained in a critical condition after being affected by COVID-19. The patient underwent three infusions of 5x107 MSCs intravenously, with an interval of three days between each session. Four days after her first cell infusion, the patient was already out of the ventilator and was able to walk. The levels of serum albumin, CRP and ALT / AST decreased, as well as other vital signs showed a significant improvement. All parameters measured, including the count of circulating T cells, neutrophils and white blood cells returned to normal levels - the lymphocytes were low, presumably due to the sequestration in the lungs and inflamed tissues. No side effects were observed[29].

CONCLUSION

Although studies involving a larger number of patients are needed, the data already published suggest that MSCs can provide a safe and effective treatment for patients who present with pneumonia resulting from SERS-CoV2 infection. The results are based on the therapeutic action of MSCs that aim to inhibit the immune system and promote tissue repair. The fact that MSCs are negative for ACE2 indicates that, after being infused into the patient, MSCs remain free of a possible infection by SERS-CoV2. After their infusion, part of the MSCs tend to accumulate in the lungs, improving the pulmonary microenvironment, protecting the epithelial cells of the alveoli and preventing pulmonary fibrosis in order to restore the function of the lungs. Thus, MSCs, through safe and effective processes for suppressing inflammatory processes and repairing lung tissue, appear as a promising therapeutic approach regarding the treatment of respiratory diseases.

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