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Stem Cell Research 52 (2021) 102239

Contents lists available at ScienceDirect

Stem Cell Research

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

Review

Medical progress: Stem cells as a new therapeutic strategy for COVID-19

Claudia Musial *, Magdalena Gorska-Ponikowska *

Department of Medical Chemistry, Medical University of Gdansk, Gdansk, Poland

ARTICLE INFO

Keywords:
SARS-CoV-2
COVID-19
Stem cells
Lung epithelial stem cells
Clinical trials
MSCs
Coronaviruses
Regenerative medicine
Pluripotent stem cells

ABSTRACT

Currently, the world is facing the SARS-CoV-2 pandemic, coronavirus of acute respiratory distress syndrome 2, causes of COVID-19. Coronaviruses are RNA single-stranded viruses that have an envelope. In addition, coronaviruses are classified into four subfamilies: alpha, beta, gamma and delta coronaviruses. The first of them, cause mildly symptomatic or asymptomatic infections, while beta-coronaviruses are responsible for severe diseases. SARS-CoV-2 belongs to the group of beta-coronaviruses. Current available therapies use corticosteroids to reduce inflammation, non-specific antiviral drugs or antibiotics in the treatment of secondary bacterial infections. In addition, therapies based on the use of hydroxychloroquine, chloroquine, remdesvir, ribavirin, interferon or lopinavir-ritonavir were also initially used. Mesenchemical stem cells (MSCs) are widely used in cell therapies, which include both basic research and clinical trials. Their exceptional effectiveness and safety have been confirmed and documented in many clinical studies, which include a number of inflammatory diseases involving the immune system – one of them is systemic lupus erythematosus. Available data indicate the ability to differentiate MSCs and their immunomodulatory effects. In addition, through interactions with immune cells, which include, but are not limited to, macrophages and dendritic cells, or paracrine secretion, MSCs are able to secrete a number of types of cytokines. MSCs are also characterized by tissue regeneration and regulation of inflammation. Due to their properties, researchers turned to determine whether MSC transplantation is able to improve the outcome of patients with COVID-19 viral pneumonia. The presented review provides not only new knowledge in the field of molecular mechanisms of pro-regenerative action of stem cells, but also have the potential to open up new prospects of action to improve lung tissue regeneration in COVID-19 patients. In addition, in review mentioned about clinical trials using MSCs with a complete status, as well as the latest discoveries in molecular biology, a platform model of pluripotent stem cells in the SARS-CoV-2 study on 3D animal models and nanoconjugates based on stem cells.

1. Introduction – COVID-19

Coronaviruses (CoV) are RNA viruses belonging to the Orthocoronavirinae family of Coronaviridae, Order Nidovirales (Cascella et al., 2020; Li et al., 2020). According to available data, the CoV genome is the largest genome of RNA viruses known to date (Cascella et al., 2020; Li et al., 2020). The CoV genome is characterized by positive envelope and single-stranded RNA. The presence of spiky glycoproteins is important on the shell. Orthocoronavirinae can be classified into four types: Alphacoronavirus (α-CoV), Betacoronavirus (β-CoV), Gammacoronavirus (γ-CoV) and Deltacoronavirus (δ-CoV). SARS-CoV-2 belongs to the β-CoV subgroup. SARS-CoV-2 is characterized by sensitivity to heat and ultraviolet radiation. Accordingly, it is known that high temperature has a significant effect on reducing viral replication. It is also worth emphasizing that SARS-CoV-2 is able to withstand temperatures below 0 °C (Cascella et al., 2020; Li et al., 2020).

SARS-CoV-2, similarly to other pathogens of the respiratory system, such as rhinovirus or influenza virus, is transmitted by droplets as a result of sneezing, coughing or speech (Cascella et al., 2020; Li et al., 2020). Particularly elevated concentrations of aerosols, which expose to potential infection, occur during prolonged exposure in confined spaces. People who are infected but do not show symptoms contribute 80% of the virus transmission. According to available data, on surfaces and objects, SARS-CoV-2 is able to survive, on cardboard boxes up to one day, on plastic up to three days, on copper surfaces up to four hours, while in the case of stainless steel, the time varies between two and three days (Cascella et al., 2020; Li et al., 2020).

The factor exacerbating the more severe course of the disease in COVID-19 patients is cytokine release syndrome (CRS) closely associated with an elevated immune response (Bhaskar et al., 2020; Huang

* Corresponding authors.
E-mail addresses: claudia.musial@gumed.edu.pl (C. Musial), magdalena.gorska-ponikowska@gumed.edu.pl (M. Gorska-Ponikowska).

https://doi.org/10.1016/j.scr.2021.102239
Received 2 January 2021; Accepted 5 February 2021
Available online 11 February 2021
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et al., 2020; Moore and June, 2020). In turn, this can lead to respiratory failure, damage to lung tissue, and even death of the patient from a cytokine storm. The clinical method of preventing excessive CRS inflammation is the use of glucocorticoid injections. However, it should be remembered that their use in the case of viral pneumonia may lead to serious consequences, such as bone necrosis (Bhaskar et al., 2020; Huang et al., 2020; Moore and June, 2020; Klok, 2020; Klok et al., 2020).

Viral infection can also lead to acute hypoxic respiratory failure, which may lead to multiorgan failure as the disease progresses, and to progressive pulmonary fibrosis, which may eventually become irreversible damage and fibrosis (Sgalla et al., 2018; Xu et al., 2020; Bian, 2020). Importantly, using electron microscopy, immunohistochemical staining and qRT-PCR methods, SARS-CoV-2 was also found in the breast, heart, kidney, skin, lymph nodes where changes in lymphoid haematopoietic organs and many other organs were noted (Sgalla et al., 2018; Xu et al., 2020; Bian, 2020).

The aforementioned cytokine storm is the leading mortality factor due to SARS-CoV-2 infection. During a cytokine storm, pro-inflammatory cytokines are released by the immune system, which simultaneously activate an increased number of white blood cells (Wu et al., 2020; Metcalfe, 2020; Liu et al., 2020; Conti et al., 2020). During the inflammatory response on a systemic scale, pro-inflammatory cytokines are secreted in the following order:

1. Tumor necrosis factor (TNFα),
2. Transforming growth factor-beta (TGF-β),
3. Granulocyte colony stimulating factor (GSCF),
4. Interleukins (IL): 1β, IL-2, IL-6, IL-7, IL-12, IL-18, IL-33,
5. Interferon-γ 10 inducible protein (IP10),
6. Monocyte chemotactic protein 1 (MCP1),
7. Interferons (IFN): IFN-α, IFN-γ (Wu et al., 2020; Metcalfe, 2020; Liu et al., 2020; Conti et al., 2020).

Inhibiting the cytokine storm inducing acute respiratory distress syndrome (ARDS) may be one of the most important elements in the treatment of COVID-19 patients (Wu et al., 2020; Metcalfe, 2020; Liu et al., 2020; Conti et al., 2020).

2. Stem cells in regenerative medicine – short review

Advances in tissue engineering allowed for the use of stem cells grown in 3D organoids adapted to personalized applications. Stem cells, while retaining the ability to self-replicate, show the regenerative effect of many different types of cells (Coronavirus, 2020; Xu et al., 2020; Guan et al., 2020). Stem cells, depending on their ability to differentiate, are ordered according to the types of cells: pluripotent, totipotent, multipotent and unipotent (Wang et al., 2020; Chu, 2004).

In addition, depending on the regenerative uses, stem cells are classified as embryonic stem cells (ESCs), mesenchymal stem cells (MSCs) (Guan et al., 2020), Wharton jelly mesenchymal stem cells (UCSC), bone marrow stem cells (BMSC), progenitor cells tissue-specific stem cells (TSPSCs) and induced pluripotent stem cells (IPSCs). Current methods of regenerative medicine using stem cells are based on tissue engineering technologies that combine microengineering and cell transplantation to develop organoids, producing the resulting tissue on biodegradable 3D scaffolds (Chu, 2004; Miossec and Kolls, 2012). Stem cell transplantation is divided into allogeneic, autologous and syngeneic. In a tissue transplant, the number of stem cells greatly influences the result of regeneration. Moreover, it is essential that the stem cells in order to survive, they should differentiate and proliferate in a manner appropriate to the site. The ability to differentiate and plasticity of cells to change the phenotype adequately in response to changes in the cellular environment are among the most important features of stem cells. Transformation of a cell into a different type of cell as well as production of cells from a differentiated stem cell known as transdifferentiation potential are equally important. It is worth noting that the aforementioned potential varies depending on from the source. Accordingly, regenerative applications are also variable (Chu, 2004; Miossec and Kolls, 2012).

One of the flagship applications of stem cells is regenerative cardiovascular therapy, due to the prevalence of heart failure among the population. Mesenchymal stem cells (MSC) were used as a therapeutic agent (Norelli et al., 2018). In 2006, an improvement in cardiac function was found in ischemic cardiomyopathy in a rabbit animal model based on autologous BMSC transplantation. Four years later, a study was published in which cord blood stem cells were transplanted in a sheep animal model. The results showed an improvement in the systolic and diastolic function of the right ventricle in heart failure. However, in 2015, positive results were demonstrated using mesenchymal umbilical cord blood stem cells (UCBMSC) in the case of disorders related to the vascular deficit (Norelli et al., 2018; Stern et al., 2018). Experimental research is also devoted to the importance of germline pluripotent stem cells (hgPSC). According to the researchers, there is a chance to induce hgPSC to create a paracrine effect on heart cells (Mahapatra et al., 2018). Importantly, the preliminary results confirm that it is possible to differentiate hgPSC into cardiomyocytes continuously and rapidly (Mahapatra et al., 2018). Moreover, researchers hypothesize that the hgPSCs that induced cardiomyocytes have a significant ability to improve heart tissue, which in turn offers an opportunity to treat heart disease (Mahapatra et al., 2018).

Another important application of stem cells in regenerative medicine is the therapy of the human eye. Diseases such as macular degeneration (AMD), retinal dystrophies, glaucoma or deficiency of corneal stem cells are treated with tissue engineering (Stern et al., 2018; Sacchetti et al., 2018). For clinical use in ophthalmology when using stem cells, includes a medical condition such as lymphoid stem cell deficiency (LSCD). So far, treatment has been based on an allogeneic or autologous conjunctival-limbal transplant or a limbal epithelial transplant. However, these treatments were associated with the risk of damage to the healthy other eye or rejection of the allograft. Consistent therapy in the case of stem cell transplantation of the cell limb, it allows the epithelium of the damaged cornea to be renewed, thus restoring the comfort of life and proper vision (Stern et al., 2018; Sacchetti et al., 2018). Research indicates that AMD Skin-iPSC-RPE and AMD RPE-iPSC-RPE, due to an increased predisposition to oxidative stress, are capable of producing higher levels of reactive oxygen species (Golestaneh et al., 2016). Researchers suggest that the SIRT1/PGC-pathways, which have a significant impact on the pathophysiology of AMD, may be a new formula for the development of drugs for targeted neurodegenerative diseases of the eye (Golestaneh et al., 2016). Researchers from the same laboratory worked on human retinal pigment epithelium (RPE) from AMD donors (Golestaneh et al., 2017). The results of developed AMD RPE cultures by macular RPE isolation from RPE donors indicate that human RPE exhibits different disease phenotypes (Golestaneh et al., 2017). In addition, mitochondrial breakdown as well as autophagosome growth were found in the cultures (Golestaneh et al., 2017). Researchers also confirmed impaired autophagy in AMD RPE by measuring the LC3-II/LC3-I ratio (Golestaneh et al., 2017). The research in particular emphasizes the mechanism of dysfunctional autophagy as the basis for the pathophysiology of the disease, which also affects the further perspective of therapeutic therapy (Golestaneh et al., 2017). Stem cells are also used as potential cancer treatment therapies, including cancer stem cells (CSCs) intended for therapeutic carriers, infusion of MSCs for post-oncological treatment, HSC transplantation intended in particular for the treatment of leukemia, lymphomas and multiple myeloma, or the production of vaccines (Chu et al., 2020). MSC expressing HSV-TK, NSC expressing CD, MSC expressing TRAIL in lung adenocarcinoma, MSC expressing INF-β dedicated to breast cancer, MSC infected with Ad5-DNX-2401 as treatment of high-grade glioma as well as MSCs infected with ICOVIR5 targeting the treatment of refractory and metastatic solid tumors, however, each of these therapies is currently registered as a

clinical trial phase I/phase II (Chu et al., 2020).

In the case of optic neuropathy, such as glaucoma, a number of types of stem cells are used, able to regenerate the optic nerve thanks to tissue engineering techniques (Alcayaga-Miranda et al., 2017). It is worth emphasizing that stem cells are a source of retinal ganglion cells (RCG), which are responsible for visual impairment as a result of damage. According to the available data, derived RCGs are a valuable source Müller stem cells from the retina. They are collected from the donor during postmortem necropsy, and then, as shown by the researchers, they are developed in vitro. This is how the immortal Müller cell line (MIO-M1) was created (Chen, 2020). Subsequently, transplantation was performed in an animal model of a rat, which proved the potential restoration of RCG in glaucoma (Alcayaga-Miranda et al., 2017; Chen, 2020).

In relation to disease entities causing inflammation and burdening the immune system's defensive ability, it is worth emphasizing the immunomodulatory effect of MSCs (Khatri et al., 2018; Waszak et al., 2012). Several studies support the anti-inflammatory effects of MSCs in animal models, which caused significant lung damage (Khatri et al., 2018; Waszak et al., 2012; Li et al., 2016; Chan et al., 2016; Curley et al., 2017; Lee et al., 2011). H5N1 and H9N2 viruses were used in the experiment (Li et al., 2016; Chan et al., 2016). The use of MSCs significantly alleviated inflammation thanks to a significant reduction in chemokines and pro-inflammatory cytokines, and also improved the image of lung tissue (Khatri et al., 2018; Waszak et al., 2012; Li et al., 2016; Chan et al., 2016; Curley et al., 2017; Lee et al., 2011).

In order to modulate immune cells, MSCs have a direct effect on proliferation as well as inhibition of T cells – both suppressing the immune response and being a major factor in the mechanism to prevent autoimmunity (Weiss and Dahlke, 2019; Harrell et al., 2020; Costela-Ruiz et al., 2020; Tan et al., 2020). As previously mentioned, the mechanism of MSCs reduces the secretion of interleukins, e.g. IL-4, or limits the proliferation of TNF-α, in this case of T-lymphocytes. It follows that MSCs can significantly improve immunity by regulating T-lymphocytes (Weiss and Dahlke, 2019; Harrell et al., 2020; Costela-Ruiz et al., 2020; Tan et al., 2020). During SARS-CoV-2 infection, the immune system becomes dysfunctional due to the induction of ARDS-mediated cytokine storms. In addition, transient lymphopenia may occur as a result of infection (Weiss and Dahlke, 2019; Harrell et al., 2020; Costela-Ruiz et al., 2020; Tan et al., 2020).

Stem cells are used in microbial infections – they inhibit drug resistance, and are also used as drug carriers (Raza and Khan, 2020; Krasnodembskaya et al., 2010; Johnson et al., 2017; Chow et al., 2020; Sutton et al., 2016; Li et al., 2020). Due to their properties, MSCs are used in the treatment of autoimmune diseases, as well as in the treatment of cystic fibrosis due to the secretion of the microbial peptide LL-37 with an antibacterial effect. In addition, they have antibacterial activity against gram-negative bacilli (Raza and Khan, 2020; Krasnodembskaya et al., 2010; Johnson et al., 2017; Chow et al., 2020; Sutton et al., 2016; Li et al., 2020).

Stem cells are also used in viral infections: influenza virus, hepatitis B virus, human immunodeficiency virus and Coxsackie B3 virus (Raza and Khan, 2020; Cotter et al., 2012; Van Linthout et al., 2011; Thanunchai et al., 2015; Wu et al., 2018). The mechanism of action of stem cells is to strengthen the immune system, reduce inflammation and the expression of interferons (Cotter et al., 2012; Van Linthout et al., 2011; Thanunchai et al., 2015; Wu et al., 2018).

3. Stem cells therapy for COVID-19

Due to their immunomodulatory properties, MSCs are increasingly used in clinical use. To date, a number of clinical trials have been conducted using the properties of MSCs in patients infected with SARS-CoV-2.

The study was carried out on seven patients with COVID-19 viral pneumonia, and three controls in Beijing using injections of umbilical cord stem cells (Chen, 2020). According to the researchers, the current data indicate that MSCs act as an anti-body agent, both through direct and indirect mechanisms, influencing the role of the immune response against pathogens. The observation period for the patients during the study was 14 days. The first reports of the use of allogeneic umbilical cord stem cells in a patient with COVID-19 infection come from China, which opened the way for further research and speculation. The therapy was carried out on a 65-year-old patient with respiratory failure and COVID-19 severe viral pneumonia caused by multiple organ systems. During the treatment, 3 doses of 50 million allogeneic umbilical cord-derived stem cells were used, 3 days apart. Stem cell therapy was used with conventional therapy to which the patient did not respond. After the application of the second dose of stem cells, the patient's vital signs were stabilized, respiratory function was no longer dependent on the ventilator, and the signs of organ failure have also normalized. After the third infusion, the patient was transferred from the ICU to the regular ward. Throat swab of the negative patient was performed 2 days after the third dose, and four days later, computed tomography was performed, which showed a significant improvement in the lung image (Chen, 2020). The satisfactory results of the study gave hope for more patients.

Another clinical trial was also published that included seven patients, including one critically and four seriously and three patients from the control group (in a serious state) (ClinicalTrials.gov, 2020). Patients were given one dose of stem cells. All patients included in the clinical trial did not respond to standard therapy. Patients were followed up for 14 days, and the entire group of seven patients treated with stem cells recovered. In the case of the control group, one patient developed ARDS and another patient died (ClinicalTrials.gov, 2020).

In analogy with other cell therapies, the use of MSCs in the therapies of the respiratory system, with particular emphasis on lung diseases, gives very quick results as a result of intravenous injection and reaches the targeted injection site, which in this case are the lungs (Harrell et al., 2019; Connick et al., 2012; Wilson et al., 2014; Saleh et al., 2020; Inamdar and Inamdar, 2013; Walter et al., 2014; Anjos-Afonso et al., 2004). As a result of interaction with capillary endothelial cells, MSCs are deposited, specifically in the vascular bed of the lungs. Clinical trials involving the infusion of MSCs clearly confirm the absence of adverse effects in response to intravenous administration (Harrell et al., 2019; Connick et al., 2012; Wilson et al., 2014; Saleh et al., 2020; Inamdar and Inamdar, 2013; Walter et al., 2014; Anjos-Afonso et al., 2004). Clinical trials involving intravenous infusion confirm the protective effect and support the modulation of the lung microenvironment as a result of COVID-19 infection, even in elderly patients (Shetty, 2020). The infusion consists in the accumulation of MSCs in the patients' lungs, which leads to the secretion of a number of paracrine factors that improve lung function and prevent their fibrosis (Shetty, 2020).

A number of reports describe the reports of scientists and doctors using allogeneic MSCs in the form of intravenous infusions (Liang et al., 2020). The available data describe a Chinese patient, 65 years of age, who, according to the current guidelines for patients infected with SARS-CoV-2, was treated with ritonavir/lopinavir, oseltamivir and IFN-α inhalation, among others (Liang et al., 2020). On the day of admission to the treatment facility, the patient's oxygen saturation was approximately 81%. After completing therapy with antiviral drugs and glucocorticosteroids, the patient received an infusion of MSCs (Liang et al., 2020). It was a fivefold infusion, 106 MSCs with each infusion. No side effects were reported as a result of the applied therapy. During the second infusion, an improvement in selected vital signs was noted, as well as an improvement in the blood serum picture – ALT/AST and CRP. Moreover, a CT scan showed an improvement in the lung picture. After the third infusion, the patient had a throat swab for SARS-CoV-2, which was negative (Liang et al., 2020).

Exosomes derived from MSCs have also been subjected to clinical trials (Walter et al., 2014). Twenty-four severely COVID-19 patients who received a 15 ml dose of ExoFlo ™ exosome agent derived from BMMSC (Bone Marrow MSC) were studied. The effect of the therapy was a

decrease in D-dimers – which are a product of the breakdown of fibrin, a protein that is involved in blood clotting, CRP and a significant improvement in the number of neutrophils (Sengupta et al., 2020). The available data indicate that exosomes (MSC-Exo), also called small extracellular vesicles produced by MSCs, due to the content of active biomolecules, may have a direct therapeutic effect, including lung diseases, diseases of the central nervous system, and also have a soothing effect on myocardial infarctions (Hassanpour et al., 2020). MSC-Exo they come from the endosomal pathway and have a diameter that oscillates between 30 and 12 nm (Hassanpour et al., 2020). It is worth emphasizing that preclinical studies have shown that MSC-Exo has a direct impact on the immune response associated with an increased cytokine storm during SARS-CoV-2 infection (Akbari and Rezaie, 2020; Tsuchiya et al., 2020). A possible therapeutic role in the course of SARS-CoV-2 infection is understood to be an increase in the secretion of anti-inflammatory cytokines, inhibition of pro-inflammatory cytokines, and regeneration of damaged tissues as a result of viral infection (Akbari and Rezaie, 2020; Tsuchiya et al., 2020). Due to the strong properties of reducing the inflammatory response, exosomes are also tested for drug nanocarriers targeting SARS-CoV-2 infection, a potential vaccine or biomarker (Akbari and Rezaie, 2020; Tsuchiya et al., 2020). Due to the content of ACE2 targeting molecules, MSC-Exo are considered potential therapeutic drugs in COVID-19 infections (Hassanpour et al., 2020).

In the treatment of SARS-CoV-2 infection, Adipose-derived mesenchymal stromal cells (AT-MSC), obtained through the liposuction method of Plastic Surgery Departments from voluntary donors, were also used (Sánchez-Guijo et al., 2020). The donors were under the age of 50, without any concomitant treatment or comorbidities. The clinical trial took place in April 2020 and included thirteen patients treated with AT-MSC. Research data indicate that one patient received three doses of AT-MSC while all other patients received two doses, and it was not felt that there was a need for more doses in infected patients (Sánchez-Guijo et al., 2020). Only one person out of thirteen patients was female. The mean number of AT-MSCs used per single dose was 0.98 (IQR 0.5) × 10 6/kg. Each patient was given prophylactic ceftrixone (an antibiotic) and low molecular weight heparin, while only steroids were administered during the administration of AT-MSC cells. After five days of administration of the first dose of cells, the vast majority of patients had a decrease in both fibrinogen and a decrease in D-dimer, and, importantly, no thromboembolic events were recorded in the patients (Sánchez-Guijo et al., 2020).

It is worth noting that MSCs have already been used in clinical trials to treat those infected with influenza A (H7N9), which had symptoms similar to those in patients infected with SARS-CoV-2, such as fever, cough, ARDS-associated dyspnoea, and pneumonia (Chen et al., 2020).

Several studies in animal models confirm the important role of the leukemia inhibitory factor (LIF) in neutralizing the cytokine storm induced by viral pneumonia (Foronjy et al., 2014; Metcalfe et al., 2015; Metcalfe, 2020). Due to the fact that MSCs release LIF, thanks to the possibilities of nanotechnology to create and generate synthetic stem cells, "LIFNano" was created (Foronjy et al., 2014; Metcalfe et al., 2015; Metcalfe, 2020). Moreover, "LIFNano" is characterized by a thousand-fold strength of action than the traditional LIF. Until now, "LIFNano" has typically been used in an experimental study of allergic encephalomyelitis (EAE) and is also used in the treatment of COVID-19 for pneumonia. The study showed the importance of LIF for the activation of epithelial STAT3, which affects the proper functioning of the alveoli (Foronjy et al., 2014; Metcalfe et al., 2015; Metcalfe, 2020). Therapy using the latest nanotechnology has a chance to be an alternative therapy to MSCs, suppressing the cytokine storm and regenerating damaged lung tissues as a result of SARS-CoV-2 infection (Foronjy et al., 2014; Metcalfe et al., 2015; Metcalfe, 2020).

The function of immunomodulation as well as low immunogenicity is also demonstrated by mesynchemal stem cells of the umbilical cord (hUC-MSC) (Shu et al., 2020). The available data show that hUC-MSCs are protective against acute lung injuries associated with avian influenza A/H5N1 virus. A pilot study has recently been conducted using hUC-MSC transplant to treat severe COVID-19 and determine the implicit therapeutic effect (Shu et al., 2020). Treatment of patients enrolled in the study included the use of antiviral drugs, invasive/non-invasive ventilation, possible antibiotic therapy and glucocorticoid therapy. An intravenous infusion was used which consisted of suspended hUC-MSC in saline. The number of cell transplants was calculated as 2 × 106 cells/kg. Twelve patients were enrolled in the hUC-MSC infusion study, while 29 patients were enrolled as a control group (Shu et al., 2020). Compared to the control group, the hUC-MSC infusion group showed marked improvement, improved dyspnoea, fatigue and chest tightness, and no invasive ventilation was required in any of the patients. However, in the case of the control group, 4 patients worsened to a critical state and invasive ventilation was required (Shu et al., 2020). No adverse effects such as infusion fever, allergic reaction or rash were reported in patients as a result of therapy with hUC-MSC infusion (Shu et al., 2020). Compared to the control group, the blood oxygenation index improved in a much shorter time (Shu et al., 2020).

Interestingly, the researchers found in patients with complications of diabetes that significantly less exogenous insulin than usual was required as a result of hUC-MSC infusions (Shu et al., 2020). The positive aspects of using infusions in patients with severe COVID-19 are clear, while the molecular mechanism of hUC-MSC action requires further studies (Shu et al., 2020).

In one clinical trial (phase I) using human umbilical cord MSCs, three patients with COVID-19 experienced side effects (Irmak et al., 2020). One patient was severely hypoxaemic within 12 h of infusion therapy, but the patient improved significantly with high flow nasal cannula (HFNC) (Irmak et al., 2020). However, in two patients the health status was moderate, one person experienced a significant reddening of the face 4 h after the MSC infusion, which resolved spontaneously after a day. Subsequently, the second patient had a temperature rise to 38 °C which also resolved spontaneously within 24 h (Irmak et al., 2020). Veno-occlusive disease (VOD), also referred to in the literature as sinusoidal obstruction syndrome (SOS), is a complication after stem cell transplantation (Bonifazi et al., 2020). In VOD/SOS, metabolic products from the liver are not removed properly. The first side effects in the form of the disease may occur in the first month after the transplant (Bonifazi et al., 2020). Further, clinical studies have shown that bone marrow MSCs with a potential profibrogenic potential can cause liver fibrosis (Lee, 2018; Musiał-Wysocka et al., 2019; Verma et al., 2020). The available data also show the growth of neoplastic tumors such as lung cancer, breast cancer, prostate cancer, gastric cancer and colon cancer (Lee, 2018; Musiał-Wysocka et al., 2019; Verma et al., 2020). Importantly, a serious infection such as interstitial pneumonia was reported in a clinical study using HSC and MSC compared to a control group of COVID-19 patients (Verma et al., 2020; Lukomska et al., 2019).

4. Effect of SARS-CoV-2 infection on lung epithelial stem cells

As is known, the COVID-19 virus can lead to severe respiratory failure by invading the lower respiratory tract. Due to multipotent stem cells, the epithelium of the respiratory tract is usually regenerated and restored as a result of the infection (Valyaeva et al., 2020). However, researchers point out that there is a possibility of SARS-CoV-2 infection of stem cells. At the same time, it leads to a more severe infection and its subsequent consequences (Valyaeva et al., 2020).

Disruption of the spontaneous regenerative activity of the lungs may occur due to infection of the epithelial stem cells (Valyaeva et al., 2020). Researchers indicate that angiotensin converting enzyme 2 (ACE2) is the input receptor for SARS-CoV-2 (Valyaeva et al., 2020). The experimental study was performed in an animal mouse model due to limited research data in the context of human lung stem cells (Valyaeva et al., 2020). Researchers performed pooled RNA-seq and single-cell RNA sequence analysis (scRNA-seq) (Valyaeva et al., 2020). BASC cells, H2-K1 cells, and AEP basal cells, or epithelial stem cells, have been shown to be

targets of SARS-CoV-2 infection. As MSCs are able to replenish the lung epithelium, an acquired COVID-19 infection may result in a severely limited ability to regenerate them properly (Valyaeva et al., 2020).

5. Platform model of pluripotent stem cells in SARS-CoV-2 study in 3D animal models

Clinical studies show a link between diabetes and COVID-19 infection (Yang et al., 2020). The authors claim that liver organoids and human pancreatic beta cells, are highly susceptible to SARS-CoV-2 infection which induced high expression of chemokines (Yang et al., 2020).

Pluripotent stem cells (hPSCs) have the ability to transform into any type of cell in the human body (Yang et al., 2020). Due to this property, researchers decided to use and develop the hPSC model as it provides similar in vivo organ models as opposed to the traditionally used 2D tumor cell lines used to study viruses. Researchers examined pancreatic endocrine cells, cardiomyocytes, endothelial cells that line blood vessels, dopaminergic neurons, and cortical neurons (Yang et al., 2020). Subsequently, it was determined whether the tested cells expressed ACE2 enzyme, which is closely related to SARS-CoV-2 infection. Using the hPSC model, the chemokine response in organoids and selected cell types was also investigated, bringing researchers closer to the reality of the impact of viral infection on tissues in COVID-19 patients (Yang et al., 2020).

6. Biomedical cell engineering – stem cell based nanoconjugates

Using the concept of cellular engineering, the conjugated nanoparticle – nanoconjungates, have been widely used in autoimmune diseases, cancer and cardiovascular diseases, as well as in the treatment of central diseases or diabetes thanks to the stimulation of T cells or NK cells and acting as regenerative drugs (Desai and Shende, 2020). Nanoconjungates are nanocarriers of active substances with a prolonged period of therapeutic action (Desai and Shende, 2020).

The resulting stem cell-based nanoconjungates are used in the therapeutic treatment of SARS-CoV-2 in the form of a nasal spray (Desai and Shende, 2020). The use of stem cells leads to the reduction of C-reactive proteins, the release of cytokines and the induction of a significant regeneration of endothelial cells and epithelial cells (Desai and Shende, 2020). In addition, the molecular mechanism of action of stem cells stimulates the release of angiopoietin-1 – a keratinocyte growth factor, which aims to remove fluid from both alveoli and microbes (Desai and Shende, 2020). Researchers used inhalation therapy using stem cells and conducted studies in animal and ex vivo models (Desai and Shende, 2020). However, in order to confirm the potential of a therapy to regenerate the lungs from COVID-19 infection, more research should be carried out using stem cell-based nanoconjungates, primarily scaling up the application or active ingredient (Desai and Shende, 2020).

7. Current clinical trials registered on the use of MSC in patients with COVID-19 with completed status

Currently, on November 23, 2020, 5 clinical trials are registered on clinicaltrials.gov using MSC treatments in patients with COVID-19 with completed status (Clinical Trials Gov, 2020):

1. Treatment With Human Umbilical Cord-derived Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19), Identifier: NCT04288102 – Tripple intravenous infusion study based on human umbilical mesenchymal stem cells (UC-MSC) (Clinical Trials Gov, 2020).
2. Use of UC-MSCs for COVID-19, Identifier: NCT04355728 – The clinical trial will consist of two infusions of UC-MCS with heparin, a blood thinner, in addition to standard COVID-19 treatment. The first infusion dose will be given within 24 h of study enrollment and the next infusion will be given within 72 h of patient enrollment in the clinical study (Clinical Trials Gov, 2020).
3. Investigational Treatments for COVID-19 in Tertiary Care Hospital of Pakistan, Identifier: NCT04492501 – Experimental clinical trial with the use of combination therapy: regenerating plasma, antiviral drugs – Tocilizumab/Remdesivir and therapy with mesenchymal stem cells, isolated from cells obtained from bone marrow (Clinical Trials Gov, 2020).
4. A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia, Identifier: NCT04276987 – A pilot clinical trial to determine the efficacy and safety of the use of aerosol inhalation of exosomes derived from allogeneic mesenchymal adipose tissue stem cells (MSCs-Exo) in patients with confirmed COVID-19 infection with pneumonia (Clinical Trials Gov, 2020).
5. Mesenchymal Stem Cells for the Treatment of COVID-19, Identifier: NCT04573270 – A clinical trial consists of a single infusion of umbilical cord stem cells used in patients with suspected COVID-19 infection, or confirmed COVID-19 infection with symptoms of respiratory diseases and fever, as well as prophylactic use in healthy people – in this case in health care workers (Clinical Trials Gov, 2020).

8. Conclusions

To sum up, for clinical use in COVID-19, umbilical cord-derived stem cells deserve special attention, especially wharton's jelly cells (Liang et al., 2020; Clinical Trials Gov, 2020; Wu and McGoogan, 2020). Contrary to bone marrow stem cells (Xu et al., 2020), they are characterized by greater plasticity and strength, and, equally importantly, they do not exhibit carcinogenic effects, as in the case of embryonic stem cells. The most frequently used method of stem cell administration in the case of coronavirus infection is intravenous infusion (Pean et al., 2019). The advantage is also the smallest invasiveness, compared to tissue or intra-arterial infusion. The safety of the therapy depends primarily on the preparation of high-quality stem cells from legal sources (Pean et al., 2019; Knoepfler, 2020). Laboratories that meet the highest standards and closely monitored and donors constantly monitored. Limitation of complications involved is mainly dependent on the use of allogeneic stem cells on the appropriate concentration and dose of cells, as well as the infusion rate (Bauer et al., 2018). Preclinical data and clinical trials indicate a potential treatment option for critically ill COVID-19 patients, but studies on a much larger group of patients should be conducted to confirm their long-term effectiveness.

Whereas it is worth mentioning, the extremely successful results of previously performed clinical trials in patients infected with SARS-CoV-2 emphasize the potential benefits of mechanical ventilation therapy with AT-MSCs (in the case of pneumonia as a complication) (Sánchez-Guijo et al., 2020), infusion of MSCs (Golestaneh et al., 2016; Harrell et al., 2019; Connick et al., 2012; Wilson et al., 2014; Saleh et al., 2020; Inamdar and Inamdar, 2013; Walter et al., 2014; Anjos-Afonso et al., 2004; Shetty, 2020; Liang et al., 2020), or hUC-MSC (Shu et al., 2020) used in cytokine storm release syndromes associated with with numerous complications and high mortality in the acute course of COVID-19 (Foronjy et al., 2014; Metcalfe, 2020a, 2020b; Bhaskar et al., 2020; Huang et al., 2020; Moore and June, 2020; Klok, 2020; Klok et al., 2020; Wu et al., 2020; Liu et al., 2020; Weiss and Dahlke, 2019; Harrell et al., 2020; Costela-Ruiz et al., 2020; Tan et al., 2020).

The above review provides not only new knowledge about the molecular mechanisms of stem cells pro-regenerative action, clinical trials based on the use of MSCs with complete status (Clinical Trials Gov, 2020a, 2020b, 2020c, 2020d, 2020e), but also summarizes the so far published knowledge on the use of stem cells in the treatment of SARS-CoV-2 infection (Chen, 2020; Khatri et al., 2018; Waszak et al., 2012; Li et al., 2016, 2020; Chan et al., 2016; Curley et al., 2017; Lee et al., 2011; Weiss and Dahlke, 2019; Harrell et al., 2020, 2019; Costela-Ruiz et al.,

2020; Tan et al., 2020; Raza and Khan, 2020; Krasnodembskaya et al., 2010; Johnson et al., 2017; Chow et al., 2020; Sutton et al., 2016; Cotter et al., 2012; Van Linthout et al., 2011; Thanunchai et al., 2015; Wu et al., 2018; ClinicalTrials.gov, 2020; Connick et al., 2012; Wilson et al., 2014; Saleh et al., 2020; Inamdar and Inamdar, 2013; Walter et al., 2014; Anjos-Afonso et al., 2004; Shetty, 2020; Liang et al., 2020; Sengupta et al., 2020; Hassanpour et al., 2020; Akbari and Rezaie, 2020; Tsuchiya et al., 2020; Sánchez-Guijo et al., 2020; Chen et al., 2020; Foronjy et al., 2014; Metcalfe et al., 2015; Metcalfe, 2020; Shu et al., 2020; Irmak et al., 2020; Bonifazi et al., 2020; Lee, 2018; Musiał-Wysocka et al., 2019; Verma et al., 2020; Lukomska et al., 2019), and also effects of SARS-CoV-2 infection on lung epithelial stem cells (Valyaeva et al., 2020), as well as the latest discoveries in molecular biology – platform model of pluripotent stem cells in SARS-CoV-2 study in 3D animal models (Yang et al., 2020) and stem cell based nanoconjugates (Desai and Shende, 2020), which offer the potential to open new prospects of action to improve lung tissue regeneration in patients with COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

MG-P acknowledges support from the Iuventus Plus project of Polish Ministry of Science and Higher Education No IP 2015 022074. CM acknowledges support from ST 46 (Medical University of Gdansk, Poland). The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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