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2022 Looking Back at COVID-19 and Stem Cell Therapy

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Abstract. The global epidemic of Corona Virus Disease 2019 (COVID-19) has been raging since its outbreak in 2019, placing enormous strain on healthcare systems all over the world. The best course of action is to prevent COVID-19 in the future, despite the fact that its virological characteristics and pathogenesis have been largely understood. And all current treatment options probably include two types: one is active immunization and the other is passive immunization. Among them, passive immunity includes supportive therapy as well as neutralizing antibodies, and small molecule drugs and other treatments are used as supportive therapy, which only slows down the symptoms and prevents complications, and then waits for the body's immune system to heal itself. On the other hand, stem cell therapy is one type of active immunity. Typically, doctors use mesenchymal stem cells (MSC) to treat patients with severe or life-threatening disorders because of their potent immunomodulatory, anti-inflammatory, and tissue healing abilities. The remarkable developments in COVID-19 stem cell therapy during the past three years are outlined in this article, along with the current state of affairs. And it was found that although stem cell therapy has been successful in stages, it still has many limitations.

Keywords: Stem cell therapy, COVID-19, Mesenchymal stem cells, SARS-CoV-2

1. Introduction

In 2019, the COVID-19 epidemic occurred all over the world, and the virus that causes COVID-19 as a coronavirus, with its extremely high infectivity and lethality, spread rapidly all over the world. As a kind of cell therapy, stem cell therapy plays a pivotal role in many diseases, so whether stem cell therapy can be applied to treat COVID-19 has become a hot issue. What advantages and disadvantages of such cell therapy compared to ordinary antibody therapy deserve to be carefully explored?

In the history of neo-crown therapy, there have been many methods, such as protein therapy, small molecule therapy, and cell therapy as brand-new therapy that needs to be clinically validated before they can be implemented. If it can be proven that stem cell therapy is useful for neo-crown, then it will open up a brand-new field in the treatment of infectious diseases. That is, the field of cell therapy. It is also a brand-new breakthrough for stem cells. In order to better understand the treatment of infectious disorders, the aim of this research is to examine the use of stem cell therapy in COVID-19.

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2. A brief introduction to stem cells and covid-19

2.1. Stem cells and mesenchymal stem cells

Fully undifferentiated or partially differentiated, stem cells have the capacity to proliferate endlessly to create more of the same type of cell or to differentiate into different types of cells. Adult stem cells are preferred in therapeutic settings due to several ethical and regulatory restrictions. Adult stem cells include mesenchymal stem cells (MSC), which are derived from adipose tissue, and hematopoietic stem cells (HSC), which are isolated from bone marrow. They have a significant capacity for tissue healing since they can multiply for a long time without differentiating into other cell types [1].

Mesodermal stem cells (MSCs) are a subclass of pluripotent stem cells that have the ability to develop into endodermal and ectodermal lineages. These comprise amniotic fluid, the amniotic membrane, and the placenta in addition to bone marrow, the umbilical cord, fat, mucosa, bone, muscle, lung, liver, and pancreas. The most prevalent MSCs come from bone marrow, adipose tissue, umbilical cord blood, and endothelial progenitor cells, but this is because the quantity and quality of stem cells in the body are not consistent. In addition, MSCs have a strong proliferative and regenerative capacity, multidirectional differentiation potential, and immunomodulatory functions. Also, MSCs are widely used in clinical applications because they are easy to isolate and collect, have stem cell properties after multiple passages and expansions, and are not ethically influenced as adult stem cells. According to several studies, the immunomodulatory properties of MSC are the most important factor in the therapeutic process [2].

2.2. COVID-19

SARS-CoV-2 is the name given to the novel coronavirus at the moment. An ongoing global COVID-19 pandemic is the result of the SARS-CoV-2 illness. According to data from the World Health Organization (WHO) website as of September 5, 2022, there are currently 600,366,479 confirmed instances of COVID-19, including 6,460,493 fatalities, and the trend is continuing to increase.According to available information, COVID-19 does not simply cause inflammation of the lungs or respiratory infections; it is a multisystem disease that causes a range of symptoms and illnesses, from mild to moderate to severe or critical.

There is currently no known medication or standard therapy for COVID-19, therefore the only available alternatives for treatment are to reduce symptoms, avoid complications, give symptomatic and supportive care as needed, and then wait for the body's immune system to repair itself. At present, researchers have developed several approaches capable of treating neo-coronavirus, which can be briefly summarized as active, as well as passive immunization. On the one hand, prevention of neo-coronavirus by vaccination worldwide; and on the other hand, treatment of patients with neo-coronavirus using small molecule drugs, neutralizing antibodies, etc. However, there are still major problems with the treatment of COVID-19 at the molecular level, such as the short half-life of the molecule and the small duration of action. As a result, scientists and clinicians around the world are still working around the clock to find new therapies. In addition to the specific drugs and therapeutic combinations currently being tried for SARS-CoV-2, there are many other treatment options. Cellular therapy is a new therapy that is distinct from molecular therapy, which has high durability, high affinity, and less immunogenicity compared to neutralizing antibody therapy. Among cellular therapies, MSC stem cell therapy, as a rising star, has already been shown in several reports as well as in experiments, and it is safe and effective [3].

3. The virus and pathogenesis of COVID-19

3.1. The COVID-19 virus: SARS-CoV-2

A beta coronavirus with an envelope and elliptical or spherical particles with a diameter of 60-140 nm is known as SARS-CoV-2. It has five key genes that target the structural proteins spike glycoprotein (S), matrix protein (M), viral envelope (E), and nucleoprotein (N), as well as RNA-dependent RNA

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polymerase (RdRp). The viral envelope (E), which is made up of proteins including matrix protein (M) and stabile protein, surrounds the nucleoprotein (N) as it forms a nucleocapsid around the RNA genome (S). The stinger proteins attach to angiotensin-converting enzyme 2 to enter the cells (ACE-2). The novel coronavirus took roughly 96 hours to be discovered in human respiratory epithelial cells after being isolated in vitro, whereas VeroE6 and Huh-7 cell lines required 4-6 days. Like other viruses, the novel coronavirus genome is prone to mutations, some of which impact the biological characteristics of the virus, such as changes in the affinity of the S protein for ACE-2, which will affect the capacity of the virus to infiltrate cells, replicate, and disseminate, the formation of antibodies during the recovery period and after vaccination, and the ability to neutralize antibody medicines, creating considerable worry. Alpha, Beta, Gamma, Delta, and Omicron are the five "variants of concern" (VOC), and the Omicron strain has now supplanted the Delta strain as the most widespread strain. The evidence that is now available indicates that the Omicron strain is less pathogenic and more transmissible than the Delta strain [3].

3.2. The general pathogenesis and progression of COVID-19

In terms of clinical studies, COVID-19 is a multisystem disease, although it mainly exhibits the characteristics of pneumonia, it causes a wide variety of different complications and produces various symptoms from mild to severe. The RNA of the new coronavirus is integrated into the cellular genome by reverse transcription to produce daughter viruses, which in turn triggers the inflammatory response, which is how the inflammatory response of COVID-19 is induced at the molecular level by the combination of the Spike protein of the new coronavirus with ACE2 of human cells [3].

According to the available information, the patient will probably go through the following processes from infection to critical condition. First, the first stage is mild, where the patient is infected. SARS-CoV-2 invades the lungs and begins to multiply. The most prevalent signs and symptoms include a dry cough, a fever, shortness of breath, myalgia, exhaustion, a sore throat, nausea, vomiting, diarrhea, conjunctivitis, anorexia, and headaches. The next stage is moderate, during which SARS-CoV-2 starts to damage the lungs' tissue structure and makes an effort to thwart the immune system before infiltrating the entire body. The patient's airways begin to fill with and accumulate debris and mucus. At this point, the patient may develop lung tissue damage, pneumonia, dyspnea, and significant lesions on chest CT. Then the third stage is severe, where SARS-CoV-2 has destroyed the lung tissue structure and begins to invade the whole body. Additionally, SARS-CoV-2 will start to interfere with the immune system's regular response, causing a cytokine storm and the related hyperimmune reaction. An unnatural systemic inflammatory response is a cytokine storm. In this case, the patient's lung tissues are damaged and multiple tissues and organs throughout the body are infected with the virus. Patients will face respiratory distress or even respiratory failure, imbalance in repair, increased inflammation, low blood oxygen reduction, and the need for assisted breathing. The last stage is critical, where SARS-CoV-2 has invaded the patient's whole body and the patient will be monitored 24 hours a day. Usually, by this time, the patient's lungs are so full of holes and filled with so much waste that a ventilator or even Extracorporeal Membrane Oxygenation (ECMO) is needed to sustain life. The patient would then experience a number of problems including acute respiratory distress syndrome (ARDS), multi-organ failure, shock, encephalopathy, myocardial infarction, heart failure, coagulation malfunction, and acute renal injury as other tissues and organs begin to deteriorate and fail one after another. Even patients who manage to survive have to worry about pulmonary fibrosis. That is the abnormal repair of the lung after damage leading to structural abnormalities and loss of function. Fibrosis cannot be reversed unless a lung transplant is performed. The average survival period after diagnosis is only 2.8 years [4, 5].

According to a German survey, COVID-19 was found to be the underlying cause of death in 86.2% of cases. The most common direct causes of death were diffuse alveolar damage (DAD) and ARDS, accounting for 52.5% of all cases; in second place was a multi-organ failure, accounting for 18%; other direct causes of death related to COVID-19 included bacterial repeat infection in 5.7% and pulmonary embolism in 4.0% of cases. In the remaining 13.8% of cases, COVID-19 was judged as a

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concomitant disease. 7.4% of cases died from circulatory diseases, such as ischemic heart disease and myocardial infarction; and 0.9% died from respiratory diseases, such as aspiration pneumonia [6].

4. Mainstream regimens and mechanisms of MSC for the treatment of COVID-19

According to the available information, the most widely used and accepted protocol is by injection, utilizing the powerful immunomodulatory, anti-inflammatory, and tissue repair functions of MSC to save critically ill or critically ill patients.

First, the COVID-19 invasion of the lung elicits a broad immune response in the body. After COVID-19 invasion, cells present the COVID-19-specific MHC antigen on the cell surface, and this presentation greatly activates dendritic cells (DCs) as a way to stimulate the immune response. T cells then secrete a very large number of cytokines to kill the virus-infected alveolar cells, while B cells respond specifically by secreting IgG antibodies to fight the virus. During the killing process of T cells and B cells, lymphocytes will keep dying, and the accumulation of dead cells will cause inflammation, and these inflammations are one of the causative factors leading to the patient's death. MSCs can interact with immune cells to activate immune regulatory responses [7, 8].

In vitro, MSC can significantly decrease T cell activation and proliferation, for instance, by a variety of soluble and cell contact-dependent mediators. These mediators can influence T cells directly or indirectly by controlling other helper cells and antigen-presenting cells. Additionally, MSCs have the ability to convert T cells from a pro-inflammatory to an anti-inflammatory state by reducing T cell IFN- and TNF-secretion and increasing T cell IL-4 secretion. By suppressing the expression of Blimp-1, preventing B cells from differentiating into plasma cells, and lowering the level of immunoglobulin overproduction, MSCs for B cells can prevent the overproliferation of B cells [1]. Second, a variety of immune cells, including antigen-presenting cells, neutrophils, and NK cells, contribute to the development of infections. It has been discovered that MSCs control them as well. For instance, macrophages and DCs are thought to be the two main antigen-presenting cells in the infection process. MSC can interfere with the antigen-presenting function of DCs, lowering DC activation and the production of inflammatory cytokines, while MSC can also modulate macrophage polarization by secreting exosomes to decrease chronic inflammation and improve tissue repair after injury. This is MSC immunomodulation's purpose [9].

In addition to its immunomodulatory functions, MSC also regulates the over-response of immune cells. During COVID-19 invasion, the body develops a cytokine storm and an associated over-immune response, even triggering ARDS. The cytokine storm causes a severe immunological imbalance in the body by abnormally activating and dysregulate the entire immune system. Such an excessive immune response attacks both normal cells and cells invaded by the virus, causing the patient to suffer. MSC has been found to significantly reduce cytokine storm, allowing the body's cytokines to return to a relatively normal level, even relieving inflammation and promoting repair [10, 11].

Another aspect contributing to MSCs' capacity for tissue healing is their capacity to secrete a wide range of growth factors and cytokines. Hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), and fibroblast growth factor are a few examples of the growth factors that MSCs might secrete to encourage cell proliferation and tissue injury healing (FGF).Moderately symptomatic as well as more severe COVID-19 patients are faced with organ tissue damage. According to the available data, MSC is not only effective in promoting lung repair, but also in promoting tissue repair in other damaged tissues, such as patients with multiple organ failure, and activating multiple repair mechanisms, such as anti-inflammatory, anti-apoptotic, inhibition of fibrosis, pro-angiogenic and pro-proliferative. In addition, since MSC was experimentally observed to reduce the levels of pro-fibrotic factors, it was found that MSC could also prevent pulmonary fibrosis. It is currently speculated that this is due to a paracrine mechanism, but this has not been confirmed. The restoration of the lung microenvironment, protection of alveolar epithelial cells, prevention of pulmonary fibrosis, and treatment of pulmonary dysfunction and lung inflammation are all possible as a result of MSC in the lung [12, 13].

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5. Conclusion

Following the COVID-19 outbreak in December 2019, as of now in September 2022. For close to three years, countless scientists, and doctors have worked tirelessly. However, the current epidemic is still recurrent and cannot be ignored. Stem cells, as a technology with high hopes, bring hope to critical patients, so I believe that with the efforts of countless researchers and doctors, we will eventually overcome the disease and usher in the dawn.

Although stem cell therapies have been successful in stages, there are still many limitations. First, stem cell therapy is not fully mature and it is difficult to obtain stem cells, so inevitably, the cost of stem cell therapy is too high. Secondly, stem cell therapy is always passive immunity, not active immunity, which is not as effective as a vaccine. Thirdly, stem cells are slow to expand and the transportation conditions are harsh. Fourthly, there is no perfect solution to the problem of immunogenicity between cells for the time being. At present, it seems that the future research direction about stem cell therapy is inclined toward the following points. Firstly, how to improve the safety of stem cell therapy. Secondly, how to reduce the production cost of stem cells and realize the rapid production and expansion of stem cells. Third, can the success of COVID-19 stem cell therapy be extrapolated to treat other infectious diseases? If so, how to make stem cell therapy apply to more infectious diseases? These are all questions that are still unclear.

6. Authors' contribution

This paper is written by three authors: Ningbo Wu, Yiting Li and Lu Luo. Ningbo Wu is the major contributor. Yiting Li and Lu Luo contributed equally. Wu constructed the framework of this paper and completed most of the writing, while Li and Luo did the literature search and organization, citation formatting, translation and proofreading, etc.

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