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Current progress of stem cell-based therapy

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Abstract: *Stem cell therapy is a promising treatment for several diseases. In this review, we summarized various cell treatments for some specific diseases, such as cell replacement therapies for Parkinsons disease. We discussed the issues and advantages of fetal neural stem cells, embryonic stem cell- and induced pluripotent stem cell-derived dopaminergic progenitors. We also described the advances and challenges for mesenchymal stem cell treatment for pulmonary fibrosis. Finally, we analyzed the potential mechanism and characteristics of stem cell therapy, and put forward prospects for the application of stem cells.*

Keywords: *stem cell therapy, neurodegeneration disease, neuroregeneration, pulmonary fibrosis*

1. Introduction

It is difficult to treat cancers and some neurological disorders using past treatments. The only need for the drugs used in the past is to depress the symptoms that caused by diseases. Stem cell-based regenerative medicine has been considered as a new hope to treat these diseases. Cell replacement is a kind of therapy based on stem cells, which is totally different from traditional therapies because it has the potential to cure diseases. Like strokes, Parkinson's disease (PD), and cancers. Scientists have developed several cell therapy strategies for the treatment of Parkinson's disease, Alzheimer's disease (AD), and stroke.

In the first part of this paper, we will introduce cell replacement therapy in two aspects, the treatment of PD and cancers. PD is caused by the lack of dopaminergic neurons in the substantia nigra pars compacta [1]. The therapies were greatly limited, medication comes with abundant negative side-effect and multiple symptoms they cannot solve, including the failure on stopping the underlying neurodegeneration, the diminishment of the effectiveness according to the development of the disease, and motor fluctuations induced by levodopa [2]. Surgical treatments were also developed to overcome the lack of medication. However, neither the medicine nor the surgery was a radical curation, they mainly focus on the reduction and relief of the symptom [2]. Since the original problem of PD is the lack of dopaminergic neurons, transplantation of dopaminergic neurons holds great potential for the restoration of neural circuitry.

Another part is about the use of stem cells in cancer treatment. NK cell is a kind of cell that have access to specific recognized old, diseased, virus-infected cells. When they are specifically recognized and binding with cells, they secret a special kind of enzyme activates the intracellular lysosome there by apoptotic. NK cells are made by the division and differentiation of lymphoid stem cells, so if we use stem cell culture technology to grow it, and stimulate it with cancer pathogens, we can quickly and efficiently induce apoptosis of cancer cells, and thus have a therapeutic effect.

Pulmonary fibrosis (PF) is a kind of disease that produces unrecoverable scar tissue inside of the lung that causes dyspnea. The expectation of life is five years, so far, there is no clear available treatment for this kind of disease except lung transportation in the later period. Mesenchymal stem cells (MSCs) seem to be a practical way, which is widely reported as an advanced new technology that cures irreversible diseases. MSCs are stem cells that be collected in various tissues in the human body and own a strong ability in tissue recovery, the exosome of MSCs is also worth utilizing. In the last part, many ways of MSCs caring for pulmonary fibrosis would be discussed.

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2. Research progress in stem cell therapy for PD

2.1 hESC-derived dopaminergic progenitors

There are several cell replacement therapies that have been proved to promote behavioral recovery in animal PD models, and some of them have successfully moved to the clinical stage. Some stem cell resources can differentiate into midbrain dopamine progenitor cells. Then, it will be transplanted into the brains of model animals, and it can project the axons to distal brain areas [3]. That is to say, the immature foreign neurons can get in touch with the host neurons, which is the basis for the treatment of neural diseases using cell replacement. Scientists try various cell resources to repair the damage in PD patients substantial nigra. From the very beginning, they use neural stem cells from fetal brain. Fetal brain-derived neural stem cells (NSCs) have a lot of advantages in the treatment of PD. Firstly, it can differentiate into nerve cells, including neurons. NSCs can also be transplanted into human brains and survive in the hosts brains [4]. However, the source of fetal NSCs is limited, because they come from aborted fetus between 6 and 9 weeks of gestational age [5]. Therefore, scientists have to find other cell sources that are more available than NSCs. Human embryonic stem cells (hESCs) is considered as a better choice due to its self-renewal and multilineage differentiation abilities [6]. Significantly, hESCs can also be differentiated into dopaminergic neurons, which are suitable for the cell therapy of PD [4]. After 20 years of development, hESCs-derived neural cells successfully recovered the motor dysfunctions of the 6-OHDA lesioned PD rat models [4, 7].

Although hESC-derived neural cells successfully treat rat and monkey PD models, there still are remaining some problems. Firstly, using the hESCs may have ethical problems, and it still contains some controversies. The basic problem is whether it is mortal to destroy an early human embryo for treating some diseases. In different countries, the legislations are different. For instance, in Italy, the research of hESCs is prohibited. Meanwhile, it is allowed in the UK [8]. Secondly, hESC-based cell replacement will cause immune rejection. Therefore, the patients should receive immunosuppressant treatment for a long time. That is the reason why scientists need to find some alternative cell sources. An attractive source is induced pluripotent stem cells (iPSCs). Using autogenous iPSC-derived neural products, immune suppression can be avoided [9].

2.2 iPSC-derived dopaminergic progenitors

iPSCs is a kind of cell reprogrammed from adult cells [10]. iPSCs shows strong differentiation ability that is comparable to hESCs. The successful generation of iPSC would be a resolution for multiple disadvantages of ESCs, mainly the issue of immune rejections. Generation of PD and other disease patient-specific iPSCs appeared in 2007 by introducing OCT4, SOX2, c-MYC, KLF4 or OCT4, SOX2, NANOG, and LIN28 in human fibroblasts existed in 2007 [11, 12]. The creation of patient-specific hiPSCs avoided multiple problems of hESC cells: ethical problems from using aborted issues, effectiveness problems related to immune rejection, and practical issues of supplement [13]. The similar pluripotency of iPSCs and ESCs allows it to overcome shortages of it, and bring potentially unlimited autologous stem cell sources [4, 13]. With these abundant advantages and prospects, iPSC-derived cells have already been used and proven to be effective in multiple experiments on rodents and primates.

In 2017, hiPSC-derived midbrain dopaminergic (mDA) progenitors transplanted into PD monkeys (Macaca Fascicularis) had survived and increased the spontaneous movement of the monkeys. Dense neurites would be extended into the host striatum by mature dopaminergic neurons, indicating the high feasibility and validity on PD patients [14]. Multiple experiments on rats emerged in 2020. By combining metabolism-regulating microRNAs with reprogramming factors, a method to generate clinical-grade iPSCs more efficiently has been invented [15]. With transplantation mDA progenitors, immature neurons, and post-mitotic neurons into immunocompromised PD mice and rats, Hiller get the result that mDA progenitors were significantly better in the effect on motor deficits, fiber outgrowth, and survival [16]. Also, since there is no tumor or disorders shown in these immunocompromised rats, no tumorigenicity or toxicity had been revealed [17].

Further than those animal experiments, clinical trials had been permitted in Japan. Takahashi in Kyoto University carried out a single-armed, non-random experiment to evaluate the safety and efficacy in the transplantation of hiPSCs into PD patients. They stereotaxically transplanted approximately 5 million cells through burr holes to the bilateral putamen. Their safety determination mainly targets two goals: “the incidence and severity of adverse events, and the presence or absence of graft overgrowth in the brain at 24 months after transplantation” [18]. If this experiment confirmed the safety and efficacy of

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iPSC-derived mDA progenitors transplantation, it will be used not only in "improving severe symptoms", but also in "delaying the advanced stage". The clinical studies registered on the ClinicalTrials.gov is summarized in Table 1.

Table 1: Cell replacement therapy of Parkinson's Disease registered on ClinicalTrials.gov

NCT NO.	Cell type	Country
NCT03128450	human fetal NSCs	China
NCT05901818	autologous induced NSC-derived DA progenitors	China
NCT05691114	human amniotic epithelial stem cells	China
NCT05635409	human ESC-derived DA progenitors	UK and Sweden
NCT05887466	human ESC-derived DA progenitors	Korea
NCT03309514	neurons-derived from adult CNS progenitors cells	America
NCT04414813	human amniotic epithelial stem cells	China
NCT03815071	autologous NSCs	China
NCT05435755	human amniotic epithelial stem cells	China
NCT02452723	human parthenogenetic neural stem cells	Australia
NCT03119636	human ESC-derived neural precursor cells	China
NCT04802733	human ESC-derived DA progenitors	America

3. NK therapy on tumors

As a result of the simultaneous mutations in the proto-oncogenes and tumor suppressor genes, enzymes that regulate cell division are altered, allowing cells to enter the division phase unchecked and thus acquire the ability to divide indefinitely. Cancer is currently a major medical problem facing humanity. Until now, researchers have worked out many ways to treat cancer, such as chemotherapy. Targeted drugs remove a portion of the cancer cells from the body and use the cell's specificity to deliver the drug to the site of the disease. And immunotherapy, which uses immune cells to kill cancer. However, scientists are looking for a new treatment with fewer side effects, and using viruses is one way, but no major progress has been made. Another is to use pluripotent stem cell-derived NK cells, to treat cancer.

NK cells, also known as natural killer cells, play an integral role in immune surveillance. NK cells are effective in limiting and preventing the appearance of cancer cells and thus preventing cancer from occurring. After cancer emerges, NK cells can specifically recognize cancer cells and play a role in cancer suppression. For the treatment of cancer. Researchers have found it could be useful in cancer treatment. Researchers discovered this, and in October 2020 the first iPSCs induced to differentiate into NK cells were grown at Chiba University and RIKEN Japan and transplanted into humans to test their safety over the next two years. Kyoto University also announced a clinical trial using iPSCs for ovarian cancer in the same year. Dr. Dan Kaufman of the University of California, San Diego, and his company successfully differentiated NK cells from iPSCs and conducted clinical trials. The trial validated the efficacy of iPSC-induced NK cell therapy against cancer and spent the next two years testing its safety.

The use of iPSCs to treat cancer is a promising line of research and we expect to see this technology develop, mature and advance over the next decade. At that point, cancer will no longer be an issue for many patients and their families.

4. Treatment of Pulmonary fibrosis with MSCs

MSCs injection showed clear evidence about the effect on pulmonary fibrosis treatment. The same mortality in both test group and control group could indicate the security of MSC treatment, a kind of therapy that though infusion bone marrow-derived MSCs clearly shown a significant effect on pulmonary fibrosis. The effect included a significant improvement on forced vital capacity and diffusing capacity of the lung for carbon monoxide in a given period with the placebo group. Animal experiments, mainly rats and mice, have exhibited high security and great potential in stem cell therapy. Ways of inducing experimental animals to pulmonary fibrosis include bleomycin, silica, paraquat, and radiation and the majority of therapy is MSCs. The most experiment of such therapy clearly indicates an increased survival rate and decreased in pulmonary fibrosis score, supporting a noticeable improvement in pulmonary fibrosis. Also, animal experiments suggest that intravenous injection could provide a better influence on the test and the environment of therapy also plays an important factor [19]. The clinical studies of cell therapy of pulmonary fibrosis registered on the ClinicalTrials.gov is summarized in Table 2.

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MSC-derived exosomes (MEx) already emerge as a practical treatment in pulmonary fibrosis. It is able to show a reverse ability in Leucomycin-induce pulmonary fibrosis, by reducing pulmonary fibrosis and collagen level to a normal level in mice models. Also, the anti-apoptosis ability of MEx is important. However, the most important role of MEx is alveolar macrophages and infiltrating monocytes regulation, which is a crucial factor in the development of pneumonia and fibrosis [20]. It is able to save cell populations in cases caused by valinomycin pulmonary fibrosis. Furthermore, MEx could show ability in stop formation of fibroblast that restrain alveolar epithelial cells proliferation.

Compare with MSCs, lung spheroid cell (LSC)-derived exosomes could make a much more distinctive influence on the repair and recovery of pulmonary fibrosis. Different from the offer of stem cells by intravenous administration, the potential of inhalation which could spread medicine to distal lung and stem cells secretome (LSC-Sec) and exosomes (LSC-Exo) is quite optimistic for the future, especially for LSCs. Researchers induce pulmonary models by Bleomycin injection and provided LSC-Sec to experiment with the effect of it. Landmarks indicate that after therapy of LSC-Sec, the situation could be improved. In addition, something worth to be noticed is that LSC-Sec showed the ability that it is able to recover the situation significantly, which is a field that cannot be achieved by MSC-Sec. LSC-Sec could reduce the magnitude of the fibrosis region and reverse the alveolar epithelial damage to healthy (sham control) level. There is a positive relationship between alveolar type 2 epithelial cells (AT2), which produce and relieve molecules important for lung defense, insult response, and homeostasis, with the LSC-Sec, suggesting the LSC-Sec could reverse the damage of epithelial damage. Moreover, the LSC-Sec and LSC-Exo could reduce Collagen deposition which would benefit to keep the cell structure [21].

Table 2: Cell therapy of pulmonary fibrosis registered on ClinicalTrials.gov

NCT NO.	Cell type	Country
NCT05468502	human umbilical cord-derived MSCs	China
NCT01919827	autologous MSCs derived from bone marrow	Spain
NCT02277145	human umbilical cord-derived MSCs	China
NCT02013700	allogeneic human MSCs	America
NCT04262167	human autologous lung stem cell	America
NCT02745184	human autologous lung stem cell	China
NCT01385644	placental MSCs	Australia
NCT05016817	allogeneic adult umbilical cord derived MSCs	America
NCT03187431	autologous bone MSCs	Egypt
NCT02135380	autologous adipose derived MSCs	India
NCT02594839	bone marrow MSCs	Russia

5. Conclusions

Stem cells have shown excellent therapeutic prospects in an increasing number of diseases, and many MSC-based studies have moved to the clinical stage. However, there are still many problems to be solved in the application of stem cells, such as in vivo integration and immune rejection of cell replacement, mechanisms of action of MSCs, regulatory and product standards for cell therapy, etc. In the near future, stem cell-based therapy will become an effective treatment method for many diseases.

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