REVIEW

Advances in cell therapy research

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ABSTRACT

Cell therapy represents an important area of biotechnology, with the potential to treat and even cure a variety of diseases that cannot be cured by traditional therapies. Cell therapy is currently a widely studied treatment in both preclinical and clinical settings, and many cell therapy products are undergoing clinical trials. This article reviews the application of cell therapy in a variety of diseases and the policy of stem cell therapy in China.

Key Words: Cell therapy, Stem cells, Immunological cells, Policy

1. INTRODUCTION

With the development of bioscience and technology, people can understand the differentiation and development process of normal cells and the genes that regulate stem cell differentiation by cultivating cells isolated from various tissues and organs of the body in vitro, which is helpful to understand the causes of diseases and develop treatment strategies, opening up a new research field of cell therapy. Cell therapy usually uses some cells with specific functions, which are obtained by bioengineering methods and/or treated by in vitro expansion and special culture, so that these cells have therapeutic effects such as enhancing immunity, killing pathogens and tumor cells, promoting tissue and organ regeneration and body rehabilitation, and then these cells are infused into the human body to treat or alleviate diseases. Cell therapy has a great research and application value in the three major fields of life science, new drug trials and disease research, and has become the focus of attention and research in the world.

Cell therapy is mainly divided into two categories: stem cell therapy and immune cell therapy. Stem cells are a kind of cells with self-renewal and differentiation potential, which can be used to be isolated, cultured, and induced differentiation in vitro from human autologous or allogeneic stem cells, which can generate new, normal, and younger cells, tissues, organs, etc., which can be transplanted into the human body through special transplantation technology for the disease treatment, in order to restore the body's function. In stem cell therapy research, the main cells studied include embryonic stem cells, tissue-specific precursor stem cells, mesenchymal stem cells (MSC), umbilical cord stem cells (UC-MSC), adipose stem cells (ADSC), bone marrow stem cells (BMSC) and induced pluripotent stem cells (iPSC).[1] At present, the vast majority of international clinical researches on cell therapy are carried out using various types of stem cells or precursor cells, and the indications include diabetes, cerebrovascular diseases, heart failure, liver cirrhosis, organ or bone marrow transplantation, spinal cord injury, Parkinson's disease, osteoarthritis, autoimmune diseases, genetic metabolic diseases and other types of diseases. Immune cell

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therapy is mainly used in the treatment of malignant tumors and solid tumors of the lymphoid and hematopoietic system, and immune cell therapy is to activate, modify and proliferate certain types of immune cells in an artificial environment in vitro and then infuse them into the human body, so that they can play the role of killing tumor cells and eliminating viruses and other pathogens. Immune cell therapy mainly includes dendritic cell/cytokine-induced killer cells[2] and adoptive cell therapy, among which ACT includes cytokine-induced natural killer cells, tumor-infiltrating lymphocytes, chimeric antigen receptor T cells (CAR-T) and T cell receptor chimeric T cells.[3]

2. Clinical application and research status of cell therapy

In recent years, with the rapid development of cell biology, especially in the stem cell research, a lot of explorations have been carried out in the field of cell therapy around the world, however, as a new type of treatment for human diseases, the exact mechanism of action of cell therapy is not clear, and the effectiveness and safety of clinical application are still the focus of attention and debate among the gloabal scientists.

2.1 Research on cell therapy for hematologic diseases

Hematologic cancers were the first diseases to be treated with cell therapy. In the mid-20^{th} century, hematopoietic stem cell transplantation (HSCT) was first used in clinical research by Professor Thomas from the Fred Hutchinson Cancer Research Center.[4] The sources of HSCT can be divided into bone marrow transplantation (autologous/allogeneic bone marrow transplantation), umbilical cord blood transplantation, peripheral blood stem cell transplantation (autologous/allogeneic peripheral blood stem cell transplantation). The transplantation protocol is selected according to the patient's own clinical conditions. However, the source of HSC is limited, and patients often delay treatment due to the lack of suitable matching. The chemotherapy is commonly used clinically, but the effect is not very satisfactory. Chimeric antigen receptor T cell therapy is a new method to identify, target and kill tumor cells by infusion of sufficient amount of CAR-T cells into patients, with a high application value and no serious adverse consequences, relatively good safety and patient tolerability, and its basic principle is that autoimmune cells can be used to remove cancerous cells.[5] Among CAR-T cell therapies, CD19 is the most common, mature and widely used, and it is well tolerated and responsive to refractory or relapsed B-cell malignancies.[6] As is known, HSCT has been already used in clinical practice, but a number of immune cell therapies represented by CAR-T are still only in phase I studies, and the sample capacity is insufficient for phase II studies. It is required to increase the number of patients to further validate the efficacy of other antigen treatments and individualize the pre-treatment protocol etc.

2.2 Research on cell therapy for cardiovascular diseases

Cardiovascular disease is a major disease that threatens human health worldwide. In terms of cell therapy for cardiovascular diseases, Dr. David M. Clifford and his colleagues from the Stem Cell Research Laboratory at the University of Oxford, England, conducted a meta-analysis of the clinical trial of 1,765 subjects with stem cell myocardial infarction in 17 countries between 2004 and 2011. The pooled results showed that this stem cell therapy significantly improved the left ventricular function, reducing left ventricular end-systolic and end-diastolic volumes, while reducing infarct area and wall activities.[7] Shiba Y et al. successfully restored the cardiac function by transplanting monkey cardiomyocytes grown from induced pluripotent stem cells (iPS cells) into the monkeys with myocardial infarction.[8] iPS cells are stem cells transformed from somatic cells after the treatment of inducing factors, and their functions are similar to embryonic stem cells. They have the potential to develop into a variety of tissue cells, which is expected to be used in regenerative medicine. Although there are a large number of studies on the efficacy of stem cells in the treatment of cardiovascular diseases, there is still controversy about their mechanism of action. Jeffery Molkentin et al. found that activation of the innate immune response was able to explain the beneficial effects of stem cell transplantation on the mouse heart. This mechanism is completely different from the "stem cell therapy that works as a repair by replacing damaged or dead heart cells" proposed more than 20 years ago. The research team confirmed that whether they injected live stem cells, dead stem cells, or zymosan (a powerful activator in the innate immune system) into the mouse heart with myocardial infarction, the improvements would be achieved in heart function. Conversely, if cyclosporine, which suppresses the innate immune system, was injected after the transplantation of stem cells, heart function in mice could not be improved. In addition, they found that stem cells and zymosan had to be injected directly into the heart tissues surrounding the infarct injury area, contrary to most previous human clinical trials, in which stem cells were administered by injection into the circulatory system (intravenous/arterial administration) due to patient safety concerns.[9] The new study has demonstrated the importance of the immune system in repairing heart damage. If the results of this study are replicated in human population, it will have a significant impact on the design of relevant clinical trials.

2.3 Research on cell therapy for liver injury diseases

In terms of liver injury diseases, there are also a series of studies that confirm the effectiveness of stem cell implantation therapy. Cao Baoqiang, Xu Ruiyun et al. studied 40 patients with cirrhotic portal hypertension and showed that the liver function and liver fibrosis serological indexes in patients in the autologous bone marrow cell transportal infusion treatment group had a significant improvement with no obvious adverse reactions, which confirmed the feasibility of stem cell transplantation.[10] Wang Songxian et al. treated 150 patients with decompensated liver cirrhosis, and autologous bone marrow-derived stem cells were transplanted into the liver through hepatic arterial catheterization, and the clinical symptoms in the patients were significantly relieved after surgery, including 138 cases (92.0%) with improved appetite and physical strength, 134 cases (89.3%) with decreased or disappeared ascites and lower limb edema, and 140 cases (93.3%) with abdominal distension. There were no recent complications associated with stem cell transplantation after surgery.[11] Terai et al. reported the clinical efficacy of peripheral venous bone marrow stem cell transplantation in 9 patients with decompensated liver cirrhosis, with a significant increase in serum albumin and total protein and a significant decrease in Child-Pugh score after 1-year follow-up visit. The liver biopsy showed a significant increase in alpha-fetoprotein and proliferation cell nuclear antigens, indicating that there was new hepatocyte being generated.[12]

2.4 Research on cell therapy for ovarian diseases

Premature ovarian failure is one of the biggest threats to the health of the female reproductive system, and mesenchymal stem cells have shown good results in the treatment of premature ovarian failure (POF). ADSCs can accelerate the POF restoration by inhibiting the apoptosis and senescence of granulosa cells, and promote hormone secretion and ovarian tissue repair. 1×10^6 ADSCs were injected as a suspension of 100 μl of PBS solution to acute and chronic chemotherapy-induced progeria ovarian rats. The results of the study showed a significant increase in body weight in ADSC-transplanted rats in comparison to the untreated progeria ovarian rats. The test results of serum samples showed that the level of ovarian hormone secretion was increased significantly after ADSC transplantation, indicating a significant improvement in fertility and hormone secretion. ADSC transplantation also improved ovarian tissue structure in progeria ovarian rats, increasing the number of primordial, primary, and mature follicles.[13]

2.5 Research on cell therapy for psychological disorders

In recent years, it has been found that mesenchymal stem cells, especially BMSC, have good efficacy in the treatment of mental disorders. BMSCs have been shown to differentiate into neuronal cells and astrocytes under both in vitro and in vivo conditions, and express their unique genes including neuronestin, glial fibrin, and biadrenocorticosteroids, ultimately achieving the effect of alleviating depressive symptoms.[14] In addition to depression models, BMSC transplantation can also alleviate depression-like symptoms caused by other disease models, such as brain injury[15] and subarachnoid hemorrhage.[16] Apart from the direct differentiation of functional cells from BMSCs, this efficacy may also be related to the endogenous repair induced by neurotrophic factors secreted by BMSCs in specific microenvironments.

2.6 Research on cell therapy for kidney diseases

Chronic renal failure is a common and frequent disease, which is a slow and progressive impairment of kidney function caused by various reasons, and eventually leads to complete loss of kidney function. Jiang et al. observed that UC-MSC treatment in 24 peritoneal dialysis patients, each patient was injected with UC-MSC twice (2×10^7/session) within three months, which was able to increase the patient's hemoglobin level, urine output and cognitive status, and reduce inflammation and increase the level of endogenous erythropoietin. UC-MSC treatment can improve the patients' renal function, and the level of serum cystatin C was significantly increased.[17] Du et al. constructed a rat model of chronic renal failure, mesenchymal stem cell pMSCs (2×10^6 cells) were isolated from peritoneal dialysate and injected to the peritoneal dialysis rats with chronic renal failure for the purpose of treatment. Compared with UC-MSCs, pMSCs were found to be more effective in protecting the peritoneum from structural changes caused by dialysate while reducing neoangiogenesis. pMSCs can also improve residual kidney function in uremic rats.[18] Another study found that the combination of human umbilical cord mesenchymal stem cells and resveratrol can better protect the function of renal podocytes, and the effect on reducing blood sugar and kidney damage is superior to that of insulin therapy, and a new method of combining stem cells and resveratrol in the treatment of diabetic nephropathy has also been found.[19]

2.7 Research on cell therapy for diabetes

Diabetes affects hundreds of millions of people worldwide. The existing treatment methods for diabetes include insulin injection, but it cannot fundamentally reverse the course of diabetes, and pancreatic islet transplantation can regulate blood sugar physiologically, but organ source and immune rejection remain to be resolved. So far, there is no good cure for diabetes. Nair's research team explored the importance of human embryonic stem cell maturation during trans-differentiation into insulin-secreting β cells. The au-

thors reproduced endocrine cell clusters by isolating partially differentiated pancreatic stem cells, transphasing them into immature β cells, rearranging them to form islet size and increasing β cell clusters (eBCs). The results showed that the physiological characteristics of eBCs were similar to those of the first generation of human β cells, including insulin response to blood glucose, calcium ion signaling, and the changes in mitochondrial potentialization. Subsequently, eBCs were transplanted into healthy mice, and it was found that eBCs could be stimulated by glucose to secrete insulin within 3 days at the earliest. Then, the corresponding insulin concentration produced by the change in blood glucose concentration was observed, and it was found that it behaved like the self-generated pancreatic islets.[20] The analysis of stem cells in the process of directed differentiation plays a key role in the treatment of diabetes. This clinical trial has been carried out on mesenchymal stem cell transplantation in 18 patients, showing the safety and efficacy of stem cells in the treatment of diabetes.[21]

2.8 Research on cell therapy for bone injury

Osteoarthritis is a common chronic disease of the musculoskeletal system that results in limited daily painful activities. Domestic scholars used UCMSC intravenous infusion (4×10^7/time) combined with anti-rheumatoid drugs to treat rheumatoid arthritis, and found that UCMSC reinfusion did not lead to obvious complications. In addition, the proportion of regulatory T cells in UCMSC patients' transfused blood was significantly increased, and the effect of a single treatment could last for 3-6 months. The study confirmed the safety of stem cell therapy and its role in systemic immunomodulation.[22] South Korean scholars administered 1.0×10^7, 5.0×10^7, 1.0×10^8 ADSCs by intra-articular injection for the treatment of osteoarthropathy, respectively. After six months of follow-up visit, it was found that intra-articular stem cell injection did not cause significant side effects, with significant cartilage regeneration observed.[23] Shadmanfar et al. used autologous BMSC intra-articular injection to treat 30 patients with rheumatoid arthritis in a randomized, triple-blind, placebo-controlled phase I and II clinical study. The results of the study showed a significant decrease in osteoarthritis index, joint stiffness and pain reduction, and a decrease in the degree of activity limitation.[24]

2.9 Research on cell therapy for wounds

In recent years, MSC has been found to play an important role in tissue injury repair, and basic and clinical studies have also confirmed that MSC can effectively promote the healing of skin wounds. Pratheesh et al. used PKH26-stained goat-derived BMSCs to treat rabbit skin injuries and found that cells derived from BMSC proliferation and differentiation existed at the wound edge and in the new tissues. Exogenous BMSCs participated in the formation of new wound edge tissues during wound healing.[25] Rasulov et al. first applied this treatment strategy to clinical practice, they performed allogeneic BMSC transplantation on a female patient with large-scale skin thermal burns (up to 40% of the injury area), and performed autologous skin grafting on the 4^{th} day after cell transplantation, and found that MSC treatment had a good adjuvant treatment effect, promoting the formation of blood vessels in the process of wound healing and shortening patients' recovery time.[26]

A large number of basic experiments have been carried out on cell therapy at home and abroad, and there are very few projects in the clinical transformation of cell therapy in China, and some projects have applied for clinical trials. As of May 2024, 87 clinical trials involving cell therapy were found on Chinese Clinical Trial Register, including 40 for blood system diseases, 19 for solid tumors, 8 for bone and joint diseases, 8 for cardiovascular and cerebrovascular diseases, 4 for respiratory diseases, 4 for skin damage treatment, 2 for liver failure, and 2 for immune system diseases. Cell therapy overcomes the limitations of conventional clinical treatments and opens up new ideas for the treatment of human diseases. At the same time, for some diseases that currently have no effective treatment, such as severe liver disease, graft-versus-host disease, renal transplant rejection, systemic lupus erythematosus, Parkinson's disease, Alzheimer's disease, etc., cell therapy may be considered as the treatment hope. There is still a lot of space for development on cell therapy researches in our country, and there are still many indications needing stem cell therapies. For instance, some foreign stem cell therapies for diseases such as ALS and Parkinson's disease have entered the late stages of clinical trials, but there is still a gap to be made in this field in China.

3. POLICIES RELATED TO THE CELL THERAPY INDUSTRY

At present, developed countries such as some European countries, the United States, Japan and South Korea attach great importance to the development of the stem cell industry and believe that the stem cell industry will be an important support for the country to continue leading the future biotechnology field. They have all introduced relatively complete stem cell industry policy systems. In 2007, the European Union promulgated the Advanced Therapeutic Medicinal Products Regulation, which came into effect on December 30, 2008. It defines gene therapy products, somatic cell therapy products and tissue engineering products as advanced therapeutic medical products. Cell therapy products refer to cells or tissues that have been processed with their biological

properties changed and can be used for the treatment, diagnosis or prevention of diseases. According to drug application, the Advanced Technology Treatment Medical Committee will review and approve the pending applications, and it will cost 1-2 years. The United States issued CFR1271 management regulations in 2001 and formally implemented them in 2005. This is the main regulation for cell therapy approval, which divides human cell tissues into two categories: PHS 351 products and PHS 361 products. PHS 351 products are products regulated under the HCT/Ps classification, including bones, ligaments, skin, dura mater, heart valves, corneas, peripheral blood stem cells, umbilical cord blood-derived precursor cells, modified autologous chondrocytes, epidermal cells on artificial synthetic matrices, sperm or other reproductive tissues. Japan revised the Pharmaceutical Affairs Law in 2013 and renamed it the Drugs, Medical Devices and Other Products Law, which was implemented in November 2014. The revision added a section on the regulation of regenerative medicine products. The Japanese Congress also recognized the shortcomings of the existing regulatory system in the field of cell therapy, and in 2013-2014, it successively issued the Regenerative Medicine Promotion Act and the Regenerative Medicine Safety Act, which provided regulatory basis for research, development and clinical application.[27]

With reference to the development experience of developed countries and combined with the actual development of Chinese stem cell industry, China has also issued a series of policies and regulations to provide a favorable policy support for the development of the stem cell industry. In 2015, the National Health and Family Planning Commission and the State Food and Drug Administration issued the "Regulations on the Management of Stem Cell Clinical Research (Trial)", which is the first management guidance document for stem cell clinical research. It stipulates aspects such as stem cell research institutions and project establishment and filing, so that the development of stem cell clinical research in China has a basis for reference. In 2017, the National Health and Family Planning Commission and the State Food and Drug Administration announced the first batch of six stem cell clinical research projects that had passed registration in their medical research registration information system. It is a good example of Chinese stem cell clinical trials being on the right track since the promulgation of the "Regulations on the Management of Stem Cell Clinical Research (Trial)". The number of projects that have completed filing has been increased rapidly since 2018, which also means that Chinese stem cell clinical trials start to get accelerated on the right track. In September 2018, Taiwan Ministry of Health and Welfare issued the "Amendment to the Administrative Regulations on the Implementation or Use of Medical Instruments for Specific Medical Technology Inspection and Testing" on cell therapy, officially opening up the clinical application of 6 cell therapies, including autologous peripheral blood stem cell transplantation, autologous immune cell therapy (including CIK, NK, DC, DC-CIK, TIL, adaptive T cell transfusion therapy), autologous adipose stem cell transplantation, autologous fibroblast transplantation, autologous mesenchymal stem cell transplantation and autologous chondrocyte transplantation. In 2019, according to the notice of new medical service price items issued by the Beijing Municipal Health Commission and the Shenzhen Municipal Development and Reform Commission, autologous chondrocyte cell transplantation, autologous cell repair of femoral head necrotic tissues, autologous cell-based tissue engineering cartilage treatment for joint cartilage injury, and platelet-rich plasma (PRP) therapy have entered the clinical application stage. In August 2020, the Center for Drug Evaluation (CDE) of the National Medical Products Administration (NMPA) issued the Technical Guidelines for Clinical Trials of Human Stem Cells and Their Derived Cell Therapy Products (Draft for Comments) to provide more targeted suggestions and guidelines for drug R&D registration applicants and researchers conducting drug clinical trials. In October 2022, the NMPA issued the Guidelines for Quality Management of Cell Therapy Products (Trial), which covers the basic planning of GMP management of cell therapy products, personnel, plants, facilities and equipment, donor screening and donor materials, materials and products, production management, quality management, product traceability system, etc., which aims to provide guidance for cell therapy product manufacturers and can also serve as an important reference for regulatory agencies to carry out various on-site inspections. On September 23 of 2023, the 4^{th} China Collaborative Innovation Platform Conference on Stem Cells and Regenerative Medicine announced Chinese first national standard for human stem cells, "Technical Specifications for the Management of Pluripotent Stem Cells in Biobanks" (standard number: GB/T 42466-2023), the release of this standard marks that China has a standard technical support for stem cell sample bank management, which is of great significance for promoting the standardization and development of stem cell research and application in China, and also provides a pilot demonstration for the formulation of subsequent relevant standards in the field of stem cells. In 2024, the National Development and Reform Commission took the lead in revising and releasing the Catalogue for the Guidance of Industrial Structure Adjustment (2024 Edition), which will be officially implemented on February 1, 2024. In this new industry guidance catalog, cell therapy drugs and cell culture are clearly included in the encouraged industry catalog, marking that

the Chinese government's attention and support for the field of cell therapy have reached a new height.

4. Perspectives on cell therapy research

Biotechnology and stem cell therapy research in developed countries in Europe and the United States started earlier, and its technology is relatively leading, and it has a comparative advantage in the industry, which is at the top of the industry. Chinese pharmaceutical industry continues to grow steadily, and the tumor cell therapy industry has a huge market potential. Since the launch of cell therapy projects in China, the state has successively formulated relevant policies to support medical institutions and tumor biotherapy enterprises, increase technology investment, and gradually promote the development of the domestic cell therapy market. The gradual liberalization of policies in various countries, the successive introduction of regulatory guidance related to stem cell therapy, and the accumulation of basic scientific research results and clinical trial data of biotechnology companies have laid a good foundation for the development of the cell therapy industry. In recent years, the state has frequently issued policies to support the development of the cell and gene therapy industry, and the regulatory model on cells and genes has gradually become clear, which has accelerated the development of Chinese cell and gene industry. The number of cell and gene clinical research projects in China is increasing, with the types of diseases involved increased as well.

Cell therapy has a broad clinical application prospect, but the clinical application of cell therapy is also faced with some challenges. At present, most clinical studies on cell therapy are still in the Phase I and II clinical stages. Many clinical studies have failed or been terminated. Some studies lack sufficient preclinical data, and their use involves certain risks. There are still some problems that need to be solved urgently: first of all, how to ensure a stable cell source and sufficient number of transplanted cells; second, how to obtain cell preservation technology to maintain cell activity; third, how to ensure the safety of cell transplantation therapy; and fourth, how to effectively improve the therapeutic effect of cell therapy.

Chinese cell therapy has a broad application market and profound scientific research accumulation. It also has a strong development momentum supported by favorable policies issued by the central government and local governments. However, there is still a long way to go to truly realize the rapid development of the cell therapy industry and benefit human welfare. On the one hand, the country needs to continue to increase investment in basic research, create a good scientific research environment, cultivate and attract world-class talents. On the other hand, enterprises need to increase their R&D efforts to make a breakthrough in the core technology of cell therapy and create an advanced automated industrialized cell production process system. At the same time, relevant regulatory authorities should further refine and improve the policies and regulations on cell therapy to guide the healthy and orderly development of the industry. It is believed that with the transformation of multiple cell therapy projects in China, Chinese cell therapy industry will usher in a development climax, and the majority of patients will soon be able to enjoy the results of new cell therapy technologies.

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Authors contributions

Fang Li: writing & editing. Quan Li: collecting data & editing. Xue Fu: collecting data. Xuewei Mao: collecting data. Lihua Hui: review. Ran An: review. Lingfeng Wang: conceptualization, review & editing.

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No additional data are available.

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