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MINI-REVIEW

Advances in Cell Therapy for Liver Regeneration

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Abstract: With the development of translational medicine, cell therapy has been applied in clinical practice, especially in the regenerative treatment of severe liver diseases. This article introduces the origin, development, and prospects of cell therapy from the aspects of liver disease treatment, history, current status, and clinical application feasibility of cell therapy. The article also points out the existing problems in the translational medical research of cell therapy. To achieve a favorable development in cell therapy, more fundamental and clinical are warranted.

Keywords: Cell therapy, Translational medicine, Liver regeneration, Hepatocyte transplantation

1 Introduction

Translational medicine is a new emerging concept that has gained much popularity in the field of biomedicine in recent years. Translational medicine involves cross-integration of different disciplines, aiming to transform basic research findings into clinical treatment and applications. As a bridge between fundamental research and clinical disciplines, translational medicine, which emphasizes performing basic research on clinical issues, is increasingly important in medical research and health industry and will certainly bring profound changes to future medical research[1-4].

The advancement in cell therapy is a typical case of the progress of translational medicine, in which cell research is applied to clinical practice. Cell therapy research has achieved encouraging results and shows broad application prospects. Cell therapy is a treatment method in which human autologous, allogeneic, or xenogeneic functional cells are returned or implanted in the human body after *in vitro* manipulation and can be used as an independent therapy or in combination with conventional surgery and chemotherapy. As an important part of regenerative medicine, the application of cell therapy is increasing in the treatment of genetic diseases, cancer, tissue damage, and diabetes, especially severe liver diseases[5-7].

2 Current treatments for liver disease

With the rapid development of the world's industry today, various causes of liver damage (biological, chemical, and physical factors) are increasing[8]. The final stage of liver disease, especially chronic liver disease, is associated with liver fibrosis and even cirrhosis. Once liver failure occurs, the condition is difficult to reverse. Thus, prevention and treatment of liver disease are becoming the main focus worldwide.

Although there are many methods for treating liver damage, there are no ideal clinical results[9]. Liver transplantation is currently the only effective treatment for end-stage liver disease, but insufficient donor sources limit its widespread use. Nowadays, the treatment

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of liver disease mainly depends on drugs, including antiviral drugs, anti-inflammatory hepatoprotective drugs, and proprietary Chinese medicines. However, most of the treatments based on the existing drugs have limited therapeutic effects. These drugs are generally single-target and may result in toxic accumulation in the body.

The treatment strategy of liver disease is mainly to promote liver cell regeneration, prevent the occurrence of fibrosis, reverse the fibrosis that has occurred, and promote the formation of normal liver tissue structure[10,11]. Cell therapy has the potential to cure various end-stage liver diseases. In recent years, it has gradually become an effective measure in the treatment of liver regeneration and rejuvenation.

3 Brief history of cell therapy and hepatocyte transplantation

Retrospectively, the history of cell therapy can date back to a 100 years ago. In 1912, the German doctor Kuettner, a pioneer in cell therapy, proposed that when organ transplantation is not feasible, the organ should be cut into small pieces, dissolved in physiological saline and injected into patients. In 1931, Paul Niehan of Switzerland used cell therapy for the first time to treat hypoparathyroidism. With the development and progress of cell biology, molecular biology, and tissue engineering, cell therapy has become a popular field in the medical world.

In 1988, Bumgardner *et al*. first proposed the concept of hepatocyte transplantation[12]. In 1993, Mito *et al*. carried out the first human liver cell transplantation technology in the world[13]. Since then, hepatocyte transplantation techniques have become a research hotspot. Through basic research and clinical application for more than 20 years, hepatocyte transplantation has proven to be an economical, effective, and minimally invasive method for the treatment of acute and chronic liver failure and hereditary hepatic metabolic diseases[14-17].

4 Current status of hepatocyte transplantation

The liver is one of the most important organs of the human body, and its structure and function are extremely complicated. End-stage liver diseases caused by various causes seriously endanger human health. Hepatocyte transplantation is the main method of liver regeneration. Hepatocyte transplantation is a cell engineering technique developed in the 1970s.

Cell therapy is fundamentally different from traditional drug therapy. Cell therapy is a protocol that extracts cells with a particular function from one or more tissues of a human body, amplifies the cells until an appropriate number and improves their function, then personalize the treatment for a particular patient. The gist of hepatocyte transplantation is to isolate and culture biologically active hepatocytes *in vitro*, and then transplant them into recipients. After transplantation, these hepatocytes will grow and proliferate and repair damaged liver or replace part of liver, which is similar to the role of normal hepatocytes. Compared with whole liver transplantation, hepatocyte transplantation has shown the advantages of minimal invasion, safety, simplicity, repeated transplantation, and low antigenicity. It is a palliative treatment for patients with liver failure waiting for donor liver[18]. Moreover, hereditary liver metabolic diseases can be directly transplanted by newly isolated hepatocytes. The hepatocytes can be genetically modified *in vitro* to become good vectors for gene therapy.

Multiple steps are required and optimized to obtain the active hepatocytes from liver tissue for transplantation. Hepatocyte isolation is the primary step. The common isolation methods include non-enzymatic cell isolation, *in vitro* liver enzymatic digestion, and *in vivo* liver perfusion. These techniques for isolating hepatocytes are widely used[19]. During isolation, precautions should be taken to reduce cell damage and maintain cell viability and adherence[20-22].

The ideal method for *in vitro* culture of hepatocytes should simulate the microenvironment of hepatocytes growing *in vivo* as much as possible, provide hepatocyte with adhesion surface, reconstruct three-dimensional cultural structure, enhance cell-cell interaction, and accelerate the exchange of nutrients and metabolites. At present, there are many *in vitro* hepatocyte culture techniques such as cell block technique for cells cultured in adherence, hepatocyte, and non-parenchymal cell mixed culture method, single collagen gel layer culture method, double collagen gel layer (sandwich) culture method, microcarrier adhesion culture method, microcapsule culture method, spherical aggregate culture method, microfluidic channel culture method, and bioreactor culture system[23]. *In vitro* hepatocyte culture is the basis of cell therapy, requiring the number and function of cells to meet the requirements of hepatocyte transplantation[24-26]. However, the current problems are that the number of transplanted cells cannot meet the requirements of transplantation after hepatocyte expansion *in vitro* because the hepatocytes are prone to apoptosis and loss of specific functions after multiple passages[27,28]. Therefore, the *in vitro* hepatocyte culture technique is not mature yet, and it needs to be further improved.

Hepatocyte transplantation requires a relatively large space to ensure that the transplanted liver cells and blood supply are sufficient. At present, hepatocyte transplantation sites mainly include portal vein, spleen, and abdominal cavity. In theory, the microenvironment of the liver itself and the nutrients in the portal vein blood are beneficial to the implanted hepatocytes. It is an ideal place for donor liver cells, but hepatocyte transplantation in the portal vein was found to cause severe thrombosis, bleeding, and other complications. The spleen is the most widely used and most mature site for liver cell transplantation[29,30]. Other than the liver and spleen, an

abdominal cavity which can provide more space, accept more cells and have fewer complications is an ideal site for liver cell transplantation[31,32]. The traditional hepatocyte transplantation is performed through intravenous injection. With the advancement of minimally invasive treatment of vascular intervention, a series of targeted interventional treatments have been developed in a clinical setting.

Currently, the cells that can be used in hepatocyte therapy research include the human primary hepatocytes, fetal liver cells, tumor-derived hepatocytes, immortalized hepatocytes, hepatic stem cells, and xenogenic hepatocytes, but most cells have short survival periods[33-37]. The cells are difficult to proliferate and expand exponentially, especially with the long culture period, and the function of hepatocytes is gradually reduced. Therefore, isolating hepatocytes that have the strong proliferative ability have become a key issue in the research field of hepatocyte transplantation. In recent years, stem cell-like hepatocytes including mesenchymal stem cells, hematopoietic stem cells, adult liver stem/progenitor cells, and embryonic stem cells have received much attention[38,39]. This is because the mesenchymal stem cells are less likely to cause immunological rejection and have significant capabilities to secrete cytokines[40]. The transplanted hepatocytes that are able to proliferate and differentiate, easy to extract and purify and amenable to large-scale *in vitro* amplification are some of the most sought-after characteristics in hepatocytes for clinical application[41]. At present, relevant research is still in the laboratory stage, and the relevant studies on the clinical application are still scanty.

5 Clinical application of hepatocyte transplantation

Hepatocyte transplantation has been applied as cell therapy which yielded favorable therapeutic effects in patients with liver disease since ten years ago[42,43]. However, the curative efficacy of hepatocyte transplantation needs to be further improved on the account of various factors such as the type of transplanted cells, immune rejection, unfavorable cell function after transplantation and proliferation disorders. To make hepatocyte transplantation more widely used in clinical settings, it is necessary to establish a more ideal system for cell isolation, purification, and culture. In addition, hepatocyte bank, cord blood bank, and stem cell bank should be constructed for the storage of important cell resources[44,45]. There are many factors that influence the success of hepatocyte isolation and culture, such as biological materials, isolation methods, culture fluids, cell density, cytoskeleton, and extracellular matrix.

To meet the needs of long-term alternative treatment, there are certain aspects that we need to address: (a) improving the survival rate of isolated hepatocyte, (b) reducing the difference in function between transplanted hepatocytes and hepatocytes *in vivo*, (c) simulating the internal environment for cell culture, and (d) reducing costs and improving efficiency of cell isolation and culture.

With the rapid development of medical science, cell therapy in liver regeneration faces opportunities and challenges in equal measure. Despite many studies performed on cell therapy showed promising results, the transformation of these findings into clinical application must be accompanied by strict supervision. In addition, more research works are still required to consolidate the techniques and therapeutic effects of cell therapy.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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