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The Functions and Characteristics of Hematopoietic Stem/Progenitor Cells Derived From Umbilical Cord Blood and its Clinical Application in Transplantation

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Abstract

Umbilical cord blood (UCB) contains abundant portable cord blood hematopoietic stem/progenitor cells (HSPCs) that can be used as a substitute to human marrow in the reconstruction of the hematopoietic and immune system. Firstly, this article expounds the functions and characteristics of hematopoietic stem cells and hematopoietic progenitor cells and the differences between UCB HSPCs and marrow HSPCs in function, then, introduces the principle of hematopoietic stem cell transplantation and the advantages and weaknesses of UCB HSPCs transplantation. The application of UCB transplantation in the clinic are also discussed.

Keywords: UCB HSPCs; Function and characteristic; Clinical transplantation

Introduction

UCB is blood that residues in the umbilical cord and placenta, and is usually discarded following child birth. In the late 1980s, physicians discovered that cord blood contained HSPCs, however it's clinical potential and significance was not recognized. It was only in 1989 that the Broxmeyer team [1]. Found that cord blood contained abundant portable HSPCs which could be used as a substitute to marrow for hematopoietic reconstruction by semi-quantitative experiments. Following this study, Gluckman et al. [2] successfully transplanted HLA UCB in children who suffered from Fanconi anemia. It proved that the UCB can be successfully applied to the clinic and can be used replace the marrow as a source of HSPCs. Since then, cord blood collection and its clinical application has increased. A large number of studies have confirmed that UCB contains abundant HSPCs and can be used for transplantation to rebuild hematopoies is and immune system function. To date this method can effectively treat more than 80 types of diseases, in particular diseases associated with the immune system and blood system.

Functions and Characteristics of UCB Hematopoietic Stem/Progenitor Cells

HSPCs consist of partial hematopoietic stem cells and a majority of hematopoietic progenitor cells. These two cells possess different characteristics that give rise to their distinct functions. Hematopoietic stem cells are a small group of the most primitive hematopoietic cells which possess multi-directional differentiation potential and high self-renewal ability. Hematopoietic stem cells can differentiate into 8 different types of cells in the hematopoietic system, including erythrocyte, neutrophil/granulocyte, monocyte/macrophage, eosinophile, basophilic granulocyte/mastocyte, megacaryocyte/soterocyte, B lymphcyte and lymphocyte T [2]. Hematopoietic stem cells always exist in the body, to maintain the quantitative and qualitative balance of all department cells and to ensure permanent hematopoietic reconstruction after transplantation.

In contrast, hematopoietic progenitor cells are a large number of hematopoietic cells that possess a reduced ability for self-renewal, but can undergo high rates of proliferation and differentiation. In the early stage, hematopoietic progenitor cells are capable of differentiating into myeloid and lymphoid progenitor cells that are able to undergo further differentiation within their own sublines to form more mature cells. These two characteristics mean hematopoietic progenitor cells are able to maintain hematopoies is and immune reconstruction function only for a short term after transplantation.

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Tabe 1: Advantages and weaknesses of UCB-HSPCs [5,6].

Advantages	1. Umbilical cord blood collection process is simple, which will not bring pain and adverse reactions to the mother and baby; 2. Umbilical cord blood is rich in HSPCs, which has good biological characteristics; 3. Umbilical cord blood contains T cells that are more immature, producing less Th1 associated cytokines than adult individuals. Simultaneously, the activity of NK cells and inhibitory T cells is weak, which may reduce the incidence of GVHD. 4.Umbilical cord blood virus (cytomegalovirus, EB virus, hepatitis virus, etc.) infection level is low 5. Unlike the too long non-related bone marrow donation cycle and the complicated uncertain factors, the storage conditions of umbilical cord blood mean it's use is more suitable and convenient for patients with acute disease or suffers from unstable conditions; 6. Unlike the short shelf-life and complex processes involved in the use of fresh donated bone marrow, umbilical cord blood storage, use, and management is relatively easy.
Weaknesses	1. Umbilical cord blood HSPCs absolute content is low, is generally only applied to children, and prone to transplant failure or delay of hematopoietic reconstruction; 2. A lower incidence of GVHD may result in a low GVL effect, which makes the recurrence rate high after transplantation; 3. When cord blood HSPCs is transplanted to an adult, there may be potential disease or adverse effects on the recipient; 4. Failure of the first transportation, and/or the recurrence of the disease will lose the remedy opportunity of restoring the donor HSPCs.

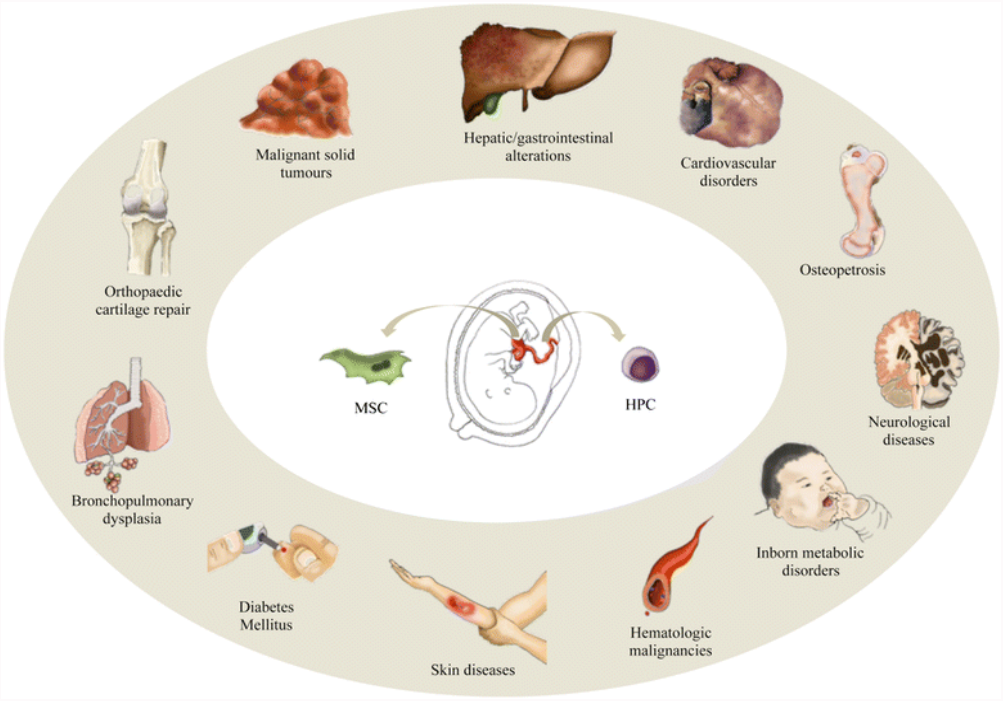

Figure 1: Clinical application of umbilical cord blood [13].

The differences in the functions of UCB HSPCs and marrow HSPCs can be attributed to the following factors [3,4]. (1) UCB HSPCs have lower maturity, longer telomeres and high telomerase activity, which confers higher proliferation potential in UCB HSPCs [2]. Compared to adult cells, UCB HSPCs have high self-renewal ability [4]. UCB HSPCs are less sensitive to inhibitory factors (such as tumor necrosis factor-a, interferon-a, etc.), but are more sensitive to stimulatory hematopoietic growth factors, so HSPCs can amplify more efficiently under the action of cytokines [4]. In the resting stage, UCB HSPCs can quickly exit the G0/G1 period (the dormant period). Any of the following mechanisms can be attributed to UCB HSPCs efficient amplification potential [5]. UCB plasma may promote cord blood cells to exit the dormant period, or high concentrations of cytokines (such as IL-6, G-CSF, etc.) in plasma may play a stimulating effect [6]. UCB HSPCs can release hematopoietic factors in an autocrine manner to promote the formation of colonies [7]. The content of lymphocyte T in cord blood is relatively small, which reduces the immunogenicity of UCB HSPCs and widens the HLA mismatch tolerance range.

Clinical Application of Umbilical Cord Blood Transplantation

Umbilical cord blood hematopoietic stem / progenitor cell transplantation

The basic principles of hematopoietic stem cell transplantation involve patients receiving high-doses of radiotherapy or chemotherapy, in combination with the use of immune suppression drugs to clear tumor cells in the host body. Autologous or allogeneic hematopoietic stem cells are then delivered to restore normal hematopoietic and immune function. Although commonly known as "hematopoietic stem cell transplantation", a more accurate term for this procedure would be hematopoietic stem / progenitor cell transplantation. From all $CD34^+$ hematopoietic stem cells isolated from three different sources (bone marrow, umbilical cord blood and peripheral blood), more than 90% are hematopoietic progenitor cells, while hematopoietic stem cells only account for a small part. Theoretically, the most ideal graft should include: hematopoietic stem cells, a large number of hematopoietic progenitor cells, stromal cells and their products.

In the process of HSPCs transplantation, two major challenges are often encountered [1,5]. Whether the donor's white blood cell antigen (HLA) is consistent with the receptor [2]. The incidence of graft versus host disease after transplantation. The feasibility of using umbilical cord blood for HSPCs grafts have been questioned by clinicians.

HSPCs transplantation can be divided into autologous and allogeneic HSPCs transplantation. Depending on the relationship between the donor and the patient, allogeneic HSPCs transplantation can be divided into blood related and unrelated donors. Although there are some advantages to autologous and blood related transplantation, difficulty finding HLA matched donors, the complexity the long cycle of the transplant process, represent some disadvantages and limit the use of the two methods in clinical practice at present.

Due to umbilical cord blood HSPCs unique biological characteristics, convenient sources and wide range of transplant adaptability, umbilical cord blood transplantation has been developed most recently over the past 30 years. Compared with traditional bone marrow transplantation, the characteristics of umbilical cord blood transplantation are shown in (Table 1).

Clinical application of umbilical cord blood transplantation

Because of the unique composition and biological features of umbilical cord blood HSPCs, and advantages of cord blood HSPCs transplantation, umbilical cord blood transplantation has been widely used in clinical practice. It's field of application has been extended to non-hematologic diseases and can also be applied for cell regeneration and immune regulation [7]. (Figure1) is current clinical trial of umbilical cord blood transplantation in the treatment of umbilical blood and non-blood type of the disease. Since the umbilical cord blood is rich in vascular progenitor cells, a 27-year-old female patient who has the Behcet multi-system disease was effectively treated by vascular graft surgery [8]. Lv et al. [9], explores the safety and efficiency in treating autistic children by combining umbilical cord blood mononuclear cells with umbilical cord blood-derived mesenchymal stem cells. The results showed that the effect of combined transplantation of the two types of cells is better than umbilical cord blood-derived mononuclear cell transplantation alone. Lima et al. [10], studied the effect of two umbilical cord blood transplantations in the treatment of adult patients with hematological malignancies, in which one umbilical cord blood contained the in vitro amplified autologous MSCs. The result showed that the combined treatment with in vitro amplified autologous MSCs can enhance the safety and efficiency of transplantation.

The disadvantages of umbilical cord blood stem/progenitor cell transplantation can be attributed to two factors [11,12], (1) The absolute amount of HSPCs and overall number of nucleated cells is is too low; this poses a major problem when more nucleated cells are required when there is a higher level of HLA mismatch. (2) After umbilical cord blood transplantation, patients are prone to relapse because of graft failure, hematopoietic delay and low incidence of GVHD. These disadvantages can be addressed by the following methods (1) *In vitro* amplification can directly amplify umbilical cord and also can isolate mononuclear cells or $CD34^+$ cells which can increase the absolute amount of HSPCs; (2) A one-time two reinfusion of umbilical cord blood or a umbilical cord blood and cell amplification; (3) Utilize modified treatment to umbilical cord blood to facilitate the homing ability of HSPCs in transplant to marrow; (4) Increase virus-specific T cells in umbilical cord blood, transducer tumor-specific diseases chimeric antigen receptor, amplify NK cells and regulatory T cells in order to prevent the incidence of relapse and GVHD; (5) Bone marrow cavity injection which can improve the homing efficiency of transplanted cells [13].

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