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Chapter 2

Current View on Hematopoiesis and Beyond

Jiaying Shen, Hongyan Tao and Zongjin Li

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Abstract

Hematopoietic stem cells (HSCs) have the ability to self-renew and give rise to all lineages of blood cells while remain the capacity of regenerative in hematopoiesis. As the only stem cell type in routine clinical use, HSCs can be isolated from bone marrow, peripheral blood and umbilical cord blood. Stem cells transplantation is mainly used in HSCs while the trans-differentiation ability broadens the research of HSCs in regenerative medicine. Here, we focus on the current view on hematopoiesis and beyond and summarize the clinical application and the regulation of the fate of HSCs. We intend to outline recent advances in the human HSCs research area and review the characteristic of HSCs from definition through development to their clinical applications and future prospect.

Keywords: hematopoietic stem cells, stem cell niche, migration, transplantation, regenerative medicine, clinical application, bone marrow, microenvironment, trans-differentiation

1. Introduction

Hematopoietic stem cells (HSCs) identification was confirmed in the 1950s after the first successful transplant was performed by Thomas et al. [1]. This transplantation involved identical twins, one of whom had leukemia. In 1968, the first major landmark in HSCs transplantation occurred with successful allogeneic transplantations [2]. In 1988, Irving Weissman et al. developed reliable methods to identify HSCs population based on a set of protein markers on the surface of mouse blood cells with flow cytometry and fluorescence-activated cell sorting (FACS) [3]. The technologic advances on HSCs researches, FACS and methods for in vitro assays have extended to the whole field of stem cell researches, such as embryonic stem cells, induced pluripotent stem cells, adult stem cells and cancer stem cells, which directly lead to fast forward the translational applications of stem cell. Four years later, Weissman lab

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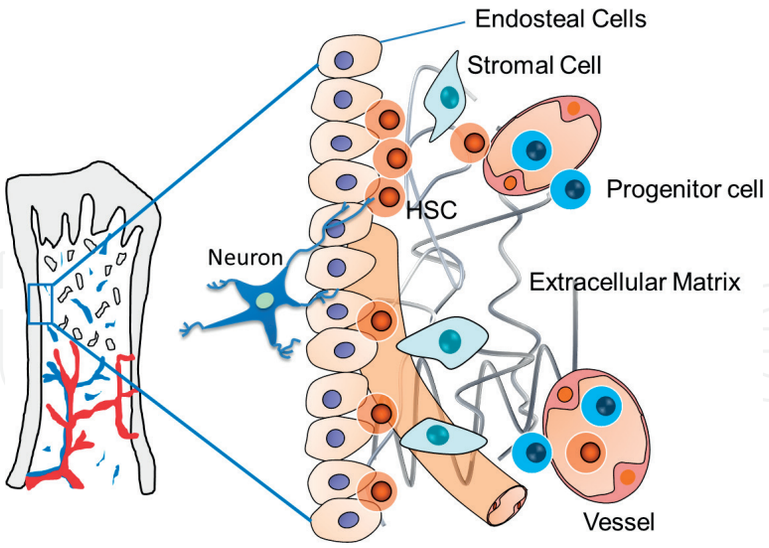

Figure 1. The model of HSCs niche. The hematopoietic niches that hematopoietic stem cells mainly reside are mainly located in the BM during adulthood. They are composed of complex components including HSCs and other functional elements such as vessels, stromal cells, ECM proteins, neural inputs and endothelial cells (ECs). Only through interaction with these components, HSCs can keep self-renewal and differentiation. Under the help of such "blocks," the progenitor cells derived from HSCs locating at the inner surface of BM migrate to blood vessels at the center of the BM cavity when they differentiate into mature blood cells. Reprinted by permission from the publisher.

proposed a comparable set of markers for the human stem cells [4]. Conceptually, human HSCs firstly appear in the earliest embryo, then move to spleen and fetal liver and ultimately migrate to bone marrow (BM) [5]. The specific microenvironments existing within the BM area have been extensively explored, which can host HSCs and other supporting cells, then further organize interaction between cells and cells and cells and growth factors in order to sustain specific aspects of hematopoiesis, such as HSCs survival, self-renewal and differentiation [6]. These special hematopoietic microenvironments are also termed as "Niche," which was first proposed by Schofield in 1978 and significant progresses have gained on hematopoietic niche [7]. Currently, it is gradually established that the main work of hematopoietic microenvironments is undertaking to support hematopoiesis (**Figure 1**). In general, HSCs are mainly maintained in BM microenvironment, which can regulate the proliferation, differentiation and mobilization of HSCs. Nonetheless, said developments in this field will throw light on hematopoietic diseases such as leukemia and aplastic anemia, rapid hematopoietic recovery after chemotherapy or shortening the time for hematopoietic reconstruction after HSCs transplantation.

2. HSCs transplantation

HSCs transplantation is most often performed for patients with malignant blood diseases, such as leukemia and multiple myeloma, or aplastic anemia, inherited blood disorders and many others. The procedure of HSCs transplantation has four steps including cell collection, patient preparation, cells transplantation and recovery. Allogeneic and autologous are the

two main types of HSCs transplantation. Allogeneic HSCs are derived from a matched donor, whereas autologous HSCs are isolated from the patients. After cell collection, patients need chemotherapy, with or without radiation to destroy the hematopoietic function and make space for the transplant. Transplantation will be proceeded with intravenous injection after patient preparation. Recovery after cells transplant can last weeks to months.

However, HSCs transplantation remains a dangerous procedure with many possible complications; it is reserved for patients with life-threatening diseases. Infection and graft-versus-host disease (GVHD) are major complications of allogeneic HSCs transplantation. A major challenge in improving the success of allogeneic hematopoietic stem cells in the treatment of leukemia is to minimize GVHD reactions and simultaneously optimize graft-versus-leukemia (GVL) reactions. Therefore, it remains to see the era of predicting biological behavior based on the knowledge of molecular mechanisms in HSCs transplantation, and how host responds to the transplanted HSCs.

3. Migration of HSCs into and out of marrow and tissues

The progress of stem cell research, along with technological innovation, has brought researchers to focus on the potential role of stem cells in regenerative medicine. Bone marrow-derived stem cells, including HSCs, can potentially restore the function of diseased or damaged tissues/organs, offering significant potential for regenerative medicine [8]. Moreover, trans-differentiation or plasticity of HSCs in repair or rejuvenation of tissues and organs have drawn focused attention [9]. It has been proposed that HSCs continue to migrate via the blood stream throughout adulthood. Continuous migration of HSCs among the organs and circulation likely fill the empty or damaged niches and contribute to the maintenance of normal organ functions and restoring degraded tissues [5, 6, 8–10] (**Figure 2**). Both tissue repair and regeneration are thought to involve resident cell proliferation as well as the selective recruitment of circulating HSCs [11]. Moreover, differentiation of HSCs into cardiomyocytes also give rise to thoughts that the HSCs population is critical for myocardium homeostasis and these repair progress after injury via reprogramming the phenotype of HSCs to induce cardiomyocyte renewal [9]. Furthermore, other HSCs transplantation models have shown that HSCs could transdifferentiate into liver, brain, skeletal muscle, kidney, intestine and many others [9]. Several studies have shown a constant exchange of HSCs between bone and peripheral blood and it has been estimated that up to 400 HSCs circulate in the blood of a mouse at any one time [12] (**Figure 2**). The efficiency of BM cell-based therapy to augment the recovery from damaged tissues depends on not only sufficient amount of stem cells but also efficient delivery of these cells to the desired target tissue. HSCs are unique in their ability to migrate to various sites, ensuring the safety and integrity of their regenerative potential.

Currently, there are some clinical trials about bone marrow-derived stem cells in clinical trial (*clinicaltrials.gov*). A number of trials are focused on the safety and efficacy of autologous/allogeneic stem cell transplantation for treatment of a diverse array of diseases (**Table 1**). The results of these trials have confirmed that HSCs injection is safe and has the capability

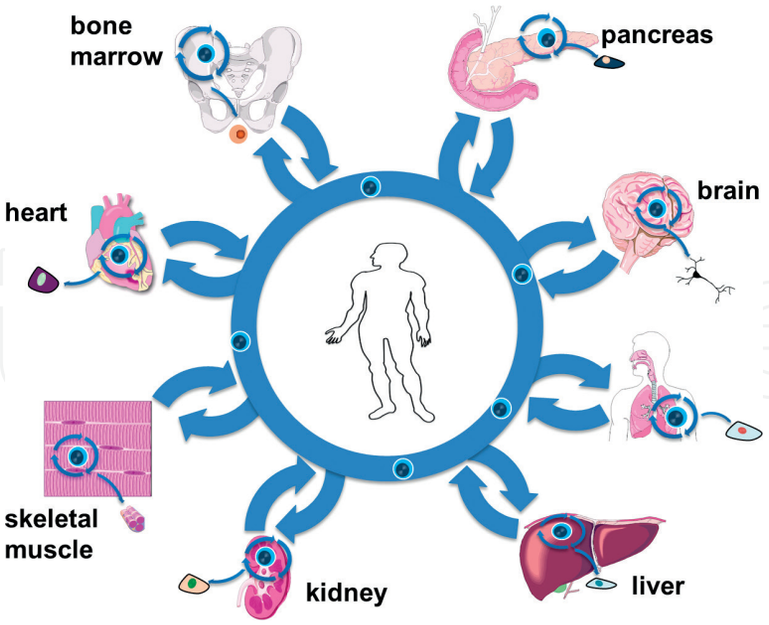

Figure 2. Maintenance and trafficking of HSCs in various tissues and organs. Besides the initial findings that HSCs are located in bone marrow, this extremely rare population of cells is also detected in other adult tissues (e.g. brain, kidney, skeletal muscle and pancreas). HSCs could be a potential back-up source for restoring the function of diseased or damaged tissues/organs. Reprinted by permission from the publisher.

Clinical study	Study phase	Source	Procedure	Year	Disease	Reference
NCT01183728	I, II	Autologous	Articular injection	2014	Knee osteoarthritis	[18]
NCT01775774	I	Allogeneic	Intravenous injection	2015	Acute respiratory distress syndrome	[19]
NCT00768066	I, II	Autologous	Transendocardial injection	2013	Ischemic heart failure	[20]
NCT00629018	II	Autologous	Intracoronary injection	2013	Dilated cardiomyopathy	[21]
NCT01363401	I, II	Autologous	Intrathecal injection	2013	Amyotrophic lateral sclerosis	[22]

Table 1. Completed bone marrow-derived stem cell-based clinical trials in regenerative medicine registered at https://clinicaltrials.gov/

to improve target tissue/organ function. However, the number of trafficking HSCs in blood stream is at an extremely low level [13]. Promoting BM stem cell mobilization is a common strategy to augment the cellular yield of peripheral blood apheresis for clinical stem cell transplantation, and a similar approach has been suggested to increase the number of circulating cells available for homing to the damaged sites following injury [10–14]. The self-renewal and trans-differentiation capacities of BM stem cells are worthless unless their migration to target tissues can be appropriately orchestrated [15].

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4. Present state of art and limitations

Allogeneic and autologous HSCs transplantation is mainly used in in the treatment of hematologic and genetic conditions. According to the data collected by Worldwide Network for Blood & Marrow Transplantation (WBMT), 953,651 HSC transplantations (553,350 [58%] autologous and 400,301 [42%] allogeneic) were reported by 1516 transplant centers from 75 countries [16] between January 1, 2006 and December 31, 2014. The use of HSC transplantations increased from the first transplant in 1957 to almost 1 million by December, 2012. This result suggests an increasing need of HSCs in clinical application. However, there are a number of challenges and limitations still confront the clinical application of HSC transplantation, such as limited HSC numbers in donor grafts and availability of HLA-matched donors. Besides, many complications such as infection, veno-occlusive disease (VOD) and GVHD after HSCs transplantation also influence quality of the patients' life, which limits its use to conditions that are themselves life-threatening. The challenges in the HSCs transplantation field are big for increasing cell survival rate after engraftment and decreasing major complications associated with a high treatment-related mortality in the recipient including infections (sepsis), GVHD and the development of new malignancies.

5. Future perspectives

HSCs are the best characterized adult stem cell type, which are mainly used in hematological disease. Several studies on HSCs biology and transplantation in their clinical therapy. Over recent years, it came as a great surprise that several models had shown that the trans-differentiation of HSCs may cross germ-layer boundaries and differentiate into some mature cells from different layer, which suggest that somatic stem cells, including HSCs, may serve as a cell source for tissue engineering or cell therapy [17]. Besides, induced pluripotent stem (iPS) cell-derived HSCs could be an ideal source for resolving current limitations related to HSCs transplantation. The use of iPS cells to generate HSCs is of considerable therapeutic interest, as traditional HSCs transplantation is limited by the lack of compatible donors, a high risk of engraftment failure and GVHD. In conclusion, these efforts could expand the use of HSCs in several different diseases, reduce the incidence of complications and increase the size of the beneficiary populations.

6. Conclusion

In conclusion, HSCs are somatic stem cells, which are vital in cell-based clinical application. After years of research, HSCs transplantation and therapy from an experimental concept to a safe clinical cure for numbers of diseases. With further study in the trans-differentiation and niche of HSCs, there is no doubt that HSCs have great prospects for application in stem cell transplantation and regenerative medicine.

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