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Review

Stem cells based transplantation for cardiovascular diseases in China

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Abstract

Stem cells based therapy has been a realistic option for cardiovascular diseases. Since 1990s, Chinese researchers and doctors have been starting to seek for optimal stem cells sources, effective methods of stem cells proliferation and differentiation with traditional Chinese medicine and clinical application of stem cells based transplantation for cardiovascular diseases. This review will summarize the investigation of stem cells in the field of cardiovascular diseases in China.

Keywords: Stem cell; Cellular transplantation; Cardiovascular disease; Chinese traditional medicine

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1. Introduction

Stem cells are undifferentiated cells with a high proliferation capacity, the capability of self-renewal, and the potential for multilineage differentiation. The concept of stem cell was formed in blood and bone marrow research in 19th century [1–3]. Research on embryonic stem cells (ESCs) derived from

Abbreviations: ESC, embryonic stem cell; EPC, endothelial progenitor cell; MSC, mesenchymal stem cell; AMI, myocardial infarction; SPECT, single photon emission computed tomography; PET, position emission tomography; MRI, magnetic resonance imaging; SFDA, state food and drug administration.

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studies on fertility and a particular tumor known as teratocarcinoma [4,5]. The first human ESCs were isolated to culture in 1998 [6]. A month later embroynoic germ cells were derived from human primordial germ cells [7]. Adult stem cells can be harvested from bone marrow, trabecular bone, periosteum, muscle, fat, brain, vascular pericytes, synovium, deciduous teeth, placenta, cord blood and skin [8–10]. Adult stem cells are being actively studied because of the current ethical and sociopolitical debate over the use of ESCs, and also because undifferentiated ESCs have been shown to give rise to teratomas and teratocarcinomas due to their unlimited proliferation capacity.

During the late 1960s successful bone marrow transplantations were reported in humans [11,12]. Today, stem cell based transplantation is a routine treatment for haematopoietic diseases. Since these first studies on stem cells, a plethora of articles have appeared on both adult and embryonic stem cells, all with the same purpose in mind: stem cells based therapy.

Cardiovascular diseases are an important cause of mortality and morbidity in the world. Many cardiovascular diseases result from a deficiency of the number of cardiomyocytes. Human cardiomyocytes are post-mitotic cells and can hardly proliferate after birth. Although a small fraction of these cells may be capable of proliferation [13], they are usually not sufficient for regeneration after myocardial injury. To treat cardiovascular diseases, cell transplantation has emerged as a potential therapy, and stem cells may be a powerful cellular source. Several approaches have been used to affect cardiomyocyte differentiation derived from stem cells and transplant differentiated cardiomyocytes into experimental animals [14–16]. Japanese researchers have cultured the cardiac cell-sheets for myocardial repair [17]. Other papers described that stem cells and endothelial progenitor cells (EPCs) could differentiate into vessel cells for vessel regeneration [18,19]. Therefore, the stem cells based transplantation has become a realistic option in cardiovascular diseases.

In China, the research on stem cells in cardiovascular field was started in 1990s. The researchers and doctors focus on differentiation of heart and vessel cells from stem cells and application of stem cells in cardiovascular diseases.

This review will summarize the investigation of stem cells in the field of cardiovascular diseases in China.

2. Stem cells sources

Embryonic and adult stem cells are frequently used in heart and vessel cells differentiation, cardiovascular tissue engineering, and cell transplantation in cardiovascular diseases. In the past years, it has been confirmed that stem cells transplantation can accelerate the myocardial and vascular regeneration, and promote the cardiac function after myocardial injury [20–23]. In 2003, Chen et al. isolated the first human embryonic stem cell lines in China [24]. ESCs can differentiate into atrium cells and ventricle cells *in vitro*, which can express the specific passage of ions and structural proteins. However, because of the current ethical and sociopolitical debate over the use of ESCs, ESCs and cardiomyocytes derived from ESCs transplantation are only applied in animal models in China. It is still a matter of debate whether and which source of stem cells will be useful for cell transplantation in the clinic. Chinese researchers have harvested adult stem cells from many tissues, such as bone marrow, peripheral blood, cord blood, trabecular bone, periosteum, muscle, fat, placenta, brain, vascular pericytes, synovium, deciduous teeth and skin [25–27]. The placenta has been affirmed as an alternative source of stem cells [8,9], which contain a population of multipotent stem cells that have some characteristics of pluripotent ES cells including expression of stem cell markers c-kit, thy-1, oct-4, ssea1, ssea3, ssea4, tra-160 and tra1-81 [12,13]. In our studies, we successfully isolated stem cells from human term placenta, which displayed two morphological types: cobblestone-like cells and fibroblast-like cells. The flow cytometry analysis showed that both cell types presented a mesenchymal stem cells (MSCs) marker profile similar to that of human bone marrow mesenchymal stem cells [28,29]. They did not express HLA-ABC and express HLA-DR at a low level, which was in contrast to BM-MSCs. Therefore, these placenta derived MSCs should be considered immune-privileged because of their potential low immunogenicity and immunosuppressive effect after transplantation [30,31]. With “Hanging drop” method placenta derived MSCs can be induced into cardiomyocytes *in vitro*. The cardiomyocyte genes *α-MHC*, *ANF* and *MLC-2v* expressed in cardiomyocytes of beating areas, and there were typical electrophysiological characteristics of three different cardiomyocyte subtypes [32]. As a waste material, the placenta is abundant from maternity wards and free from ethical concerns, which makes it superior compared with embryonic stem cells and bone marrow mesenchymal cells. Thus, placenta derived MSCs have a very promising application potential, since they may be used for regenerating pericardium tissues and serving as seed cells for tissue engineering.

In China, only stem cells derived from human bone marrow, peripheral blood and cord blood were applied in clinical trials [33].

3. The application of traditional Chinese medicine in stem cell proliferation and differentiation into heart and vessel cells

It is still an investigative hotspot how to improve cardiovascular cells differentiation from stem cells. Chinese researchers try to induce the cardiomyocytes and endothelium cells differentiation with chemical (e.g. 5-Azacitidine, ratinoic acid, TGF-β, etc.) or co-culture methods [34–37].

Traditional Chinese medicine has a 5000-year history, which is characterized by its safety and long-term effect in clinic. It can prevent myocardial ischemia by expanding