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Review

Mesenchymal stem cell therapy for heart disease

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ABSTRACT

Mesenchymal stem cells (MSC) are adult stem cells with capacity for self-renewal and multi-lineage differentiation. Initially described in the bone marrow, MSC are also present in other organs and tissues. From a therapeutic perspective, because of their easy preparation and immunologic privilege, MSC are emerging as an extremely promising therapeutic agent for tissue regeneration and repair. Studies in animal models of myocardial infarction have demonstrated the ability of transplanted MSC to engraft and differentiate into cardiomyocytes and vascular cells. Most importantly, engrafted MSC secrete a wide array of soluble factors that mediate beneficial paracrine effects and may greatly contribute to cardiac repair. Together, these properties can be harnessed to both prevent and reverse remodeling in the ischemically injured ventricle. In proof-of-concept and phase I clinical trials, MSC therapy improved left ventricular function, induced reverse remodeling, and decreased scar size. In this review we will focus on the current understanding of MSC biology and MSC mechanism of action in cardiac repair.

Contents

1. Introduction

The ability to mobilize and activate endogenous stem/progenitor cells in diseased organs or to introduce exogenous stem cells for tissue regeneration/repair may impact many diseases, including those affecting the brain, the skeletal muscle, the pancreas and the heart. The reports that embryonic and adult stem cells (ASC) can differentiate into cardiomyocytes (CMC), vascular smooth muscle cells (VSMC) and endothelial cells (EC) have stimulated studies investigating the use of stem cells as regenerative therapy for cardiovascular disease.

Abbreviations: MSC, mesenchymal stem cells; hMSC, human mesenchymal stem cells; mMSC, murine mesenchymal stem cells; ASC, adult stem cells; CMC, cardiomyocytes; VSMC, vascular smooth muscle cells; EC, endothelial cells; CHF, congestive heart failure; BM, bone marrow; AMI, acute myocardial infarction; CFU-F, colony forming unit fibroblasts; CM, conditioned medium; C-CM, concentrated conditioned medium; CSC, cardiac stem cells; I/R, ischemia/reperfusion; GMP, good manufacturing practice.

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Regenerative and reparative therapies would be particularly important for heart disease since, despite many recent advances in medical therapy and interventional techniques, ischemic heart disease and congestive heart failure (CHF) remain major causes of morbidity and mortality (Kannel, 2000; Mosterd and Hoes, 2007). The current therapeutic approaches to treat CHF merely delay the progression of the disease (Bramucci et al., 2002; McMurray and Pfeffer, 2005), thus generating a population of chronically ill patients. Heart transplantation is the only effective therapy for this otherwise deadly clinical condition. However, the limited number of organs donated is not enough to treat all patients who would require a transplant. Consequently, the disability of a growing number of people with heart disease will continue to place a heavy burden on already financially strained healthcare systems, with incalculable socio-economic costs. Cell therapy for treating these and other heart conditions is a growing field of basic and clinical research. Here we examine the basic foundation of ongoing or future clinical approaches to ASC therapy for heart diseases. In particular, we will focus our attention on mesenchymal stem cells (MSC), dwelling on mechanisms through which MSC can repair damaged hearts.

2. Mesenchymal stem cells for cardiac repair

Much of the research in cardiovascular regenerative therapies, both in animals and humans, has been conducted using bone marrow (BM)-derived stem cells. In particular, it has been demonstrated that the administration of BM-MSC can rescue damaged hearts and improve cardiac function in animal models of acute myocardial infarction (AMI) and improve vasculogenesis in chronic ischemia models (Quevedo et al., 2009).

The BM stroma was originally thought to function mainly as a structural support for the hematopoietic stem and progenitor cells in the BM (Dexter et al., 1977). It is now clear that a heterogeneous population of cells including fibroblasts, adherent stromal cells, adipocytes, EC, and osteogenic cells compose the stroma. In the 1960s Ernest A. McCulloch and James E. Till first revealed the clonal nature of marrow stromal cells (McCulloch and Till, 1960; Till and McCulloch, 1961). In the 1970s Friedenstein and colleagues reported an *in vitro* assay for examining the clonogenic potential of marrow stromal cells (Friedenstein et al., 1968, 1970) and referred to them as colony forming unit-fibroblasts (CFU-F). Subsequent experiments revealed the multipotentiality of marrow cells and how their fate was determined by environmental cues (Pittenger et al., 1999). In particular, these cells can differentiate into osteoblasts, chondrocytes, adypocytes, tendons and muscle.

Since stromal cells showed self-renewal, differentiation, and characteristics typically associated with stem cells, many investigators referred to cultured stromal cells as MSC (Fig. 1). These cells are rare, and exist at an estimated frequency of about 1 in 100,000 BM cells (Pittenger and Martin, 2004). However, the MSC can be isolated and expanded *ex vivo*, primarily taking advantage of their specific capacity to adhere to plastic surfaces.

MSC in cell culture have been characterized using a panel of specific antibodies; however there is still a lack of consensus on the definition of MSC, since the medium and serum used to culture the cells, the plating density, as well as the oxygen tension may all affect their phenotype. In general, it is well accepted that human MSC (hMSC) lack expression of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR surface molecules, while they do express SH2 (CD105), SH3 and SH4 (CD73), CD90, CD29 and CD166 (Pittenger et al., 1999; Dominici et al., 2006). Aside from this consensus in terms of surface antigen expression, the precise phenotype of hMSC is still debated, and their identification prior to culture remains ambiguous.

Peculiar characteristics make MSC interesting for cell therapy and tissue engineering purposes. For example, MSC can be isolated, expanded *ex vivo*, and used in an autologous fashion, avoiding the problem of finding a compatible donor. Furthermore, several lines of evidence suggest that MSC may not be subject to allogeneic rejection in human and animal models (Pittenger and Martin, 2004; Ryan et al., 2005). Three main mechanisms seem to contribute to such immunoprivileged profile. First of all, MSC are hypoimmunogenic, since they

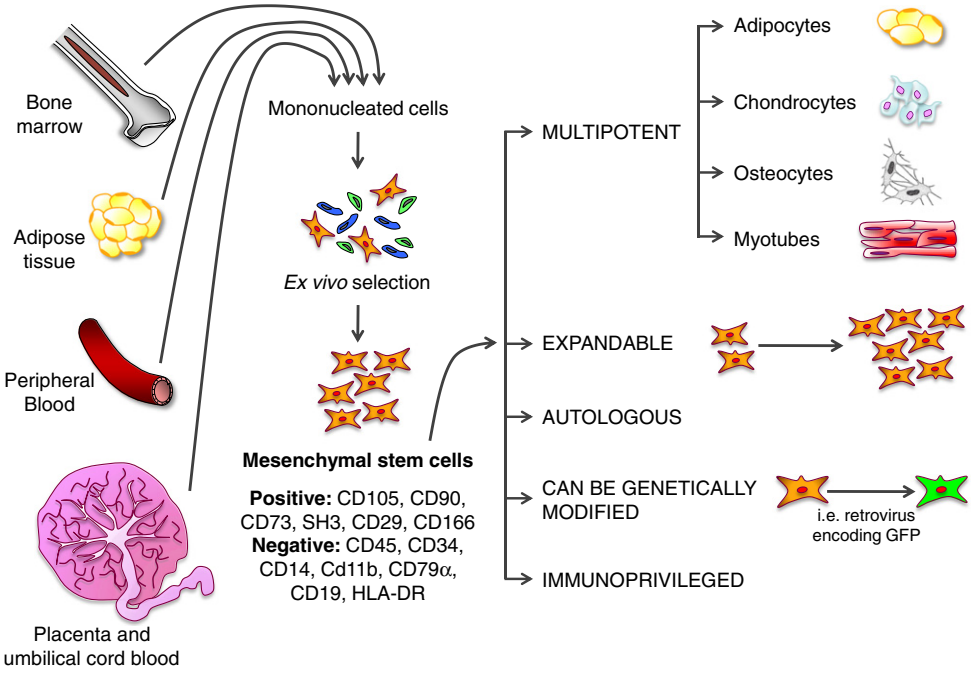

Fig. 1. Mesenchymal stem cells (MSC). MSC can be isolated from the bone marrow, adipose tissue, placenta and umbilical cord blood. Some investigators also described MSC in the peripheral blood. MSC can be expanded *ex vivo*, are multipotent and possess other favorable characteristics that make them suitable for cell therapy and myocardial repair (see text for details).