Cytotherapy, 2015; 17: 796–802

International Society for Cellular Therapy
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Novel clinical uses for cord blood derived mesenchymal stromal cells

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Abstract

Regenerative medicine offers new hope for many debilitating diseases that result in damage to tissues and organs. The concept is straightforward with replacement of damaged cells with new functional cells. However, most tissues and organs are complex structures involving multiple cell types, supportive structures, a microenvironment producing cytokines and growth factors and a vascular system to supply oxygen and other nutrients. Therefore repair, particularly in the setting of ischemic damage, may require delivery of multiple cell types providing new vessel formation, a new microenvironment and functional cells. The field of stem cell biology has identified a number of stem cell sources including embryonic stem cells and adult stem cells that offer the potential to replace virtually all functional cells of the body. The focus of this article is a discussion of the potential of mesenchymal stromal cells (MSCs) from cord blood (CB) for regenerative medicine approaches.

Key Words: *cord blood, mesenchymal stromal cell, regenerative medicine, stem cell biology*

Introduction

The use of mesenchymal stromal cells (MSCs) is a promising strategy in the treatment of many diseases. MSCs give rise to mesodermal tissue types including bone, cartilage, tendon, muscle, and fat [1,2] and are capable of modulating immune response and inflammation [3–6]. MSCs also secrete factors that stimulate stem cell engraftment, tissue repair, and vessel formation [1,7]. One advantage of MSCs is that histocompatibility matching is not required because they do not express human leukocyte antigen (HLA) class II histocompatibility antigens or CD40, CD80 and CD86, required for immune cell activation [4]. MSC chemotactic response and homing to sites of inflammation has been demonstrated in a number of animal models of injury including cerebral ischemia [8], total-body irradiation (TBI) [9,10] and myocardial infarction [11,12]. Once at the site of injury or inflammation, it has been proposed that MSCs modulate the inflammatory response and aid tissue repair of the affected organs. In this review, we seek to outline the advantages, disadvantages, current clinical trials and future studies of MSCs derived from cord blood (CB) and cord tissue (CT).

MSCs

MSCs were recognized by Friedenstein, who isolated cells from guinea pig bone marrow that were adherent in culture and differentiated into bone [13]. Surface antigens have been reported for identification and phenotyping of human MSCs [14–16]. Although MSCs are rare, representing approximately 0.01% of the bone marrow (BM) mononuclear cell fraction, they have attractive features for therapy, including the ability to expand many log-fold *in vitro*, and unique immune characteristics, allowing their use as an allogeneic graft. They are typically isolated based on adherence to standard tissue culture flasks. Low-density BM mononuclear cells (MNCs) are placed into culture in basal media plus fetal bovine serum (typically 20%), and after 2 to 3 days, adherent cells can be visualized on the surface of the flask. The nonadherent cells are removed at this time and fresh media added until a confluent adherent layer forms. The MSCs are harvested by treatment with trypsin and further passaged expanding the number of MSCs. A number of cell populations have been isolated using various culture conditions; however, the morphology of these cells is similar. Phenotypical characterization of MSC has been

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(Received 28 February 2015; accepted 2 March 2015)

ISSN 1465-3249
http://dx.doi.org/10.1016/j.jcyt.2015.03.612

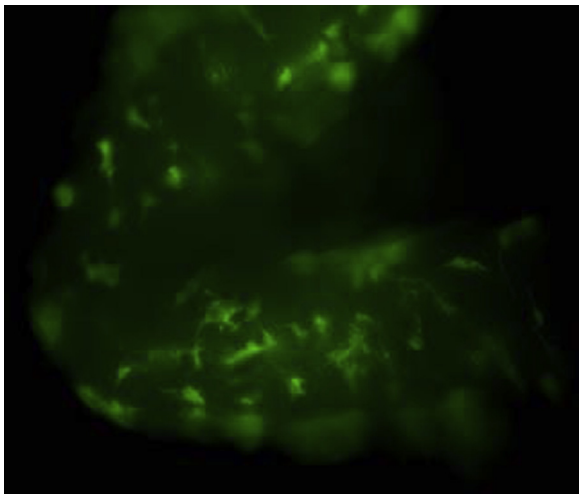

Figure 1. GFP+MSCs growing on bioscaffold.

performed by many groups, and a standard criteria has been proposed by the International Society of Cellular Therapy (ISCT) [17]. The minimal criteria proposed to define human MSCs by the Mesenchymal and Tissue Stem Cell Committee of the ISCT consists of the following: (i) the MSC must be plastic-adherent when maintained in standard culture conditions; (ii) MSCs must express CD105, CD73 and CD90, and there must be a lack of expression of CD45, CD34, CD14 or CD11b, CD79 alpha or CD19 and HLA-DR surface molecules; and (iii) MSCs must differentiate into osteoblasts, adipocytes and chondrocytes *in vitro* [17].

A standard *in vitro* assay for MSCs is the colony-forming unit fibroblast (CFU-F) assay [18] (Figure 1). MNCs are plated at low density, and colonies of fibroblasts develop attached on the surface of the culture dish. Based on the results of this assay, the frequency of MSC precursor cells is one in 10^4 to 10^5 MNC. Other studies have demonstrated that MSC precursors can be isolated based on surface antigen expression. Antibodies to CD271 and Stro-1 have been used to enrich MSC precursors. CD271, also known as low-affinity nerve growth factor receptor (LNGFR) or p75NTR, belongs to the low-affinity neurotrophin receptor and the tumor necrosis factor receptor superfamily. Selection of CD271+ cells from human BM enriches CFU-F and MSC are preferentially selected in the CD271+ fraction compared with the CD271− fraction [14,15]. Similarly, isolation of Stro-1+ cells from BM MNC results in enrichment of CFU-F in the Stro-1+ fraction compared with the Stro-1− fraction [16]. The content of CD271+ and Stro-1+ cells in CB has not been reported.

Many studies of MSCs have evaluated culture expanded MSCs; however, it is not known whether *in vitro*-generated MSCs are identical to freshly isolated MSCs—that is, CD271+ cells or Stro-1+ cells. It is possible that culture expansion limits the potential of MSCs to basic lineages described extensively for MSCs—namely, adipocyte, chondrocyte and osteoblast differentiation. Further studies are needed to define the full differentiation capacity of freshly isolated CD271+ and Stro-1+ cells and the quantity and quality of these cell populations in CB and CT. Pathways of differentiation follow adipogenic, osteogenic and chondrogenic lineages and have been reported in derail in previous publications [19–21].

CB and CT as a source for MSCs

CB is a rich source of hematopoietic stem and progenitor cells (HSCs and HPCs), which have been used a stem cell graft for cancer patients undergoing high-dose chemotherapy [22]. In addition, CB is a source of MSCs [23]. However, the frequency of MSCs is low, and only a third of CB cells provide a source for generation of MSCs *in vitro*. Alternative approaches for isolation of MSCs have been developed from the CT [24]. In fact some CB banks now routinely store both CB and CT, offering a unique and potentially advantageous source of HSCs, HPCs and MSCs from a single matched source. CB-derived MSCs have been shown to have similar biological characteristics compared with BM-MSCs but have higher proliferation capacity and lower

Table I. Comparison of CB versus BM MSCs.

	CB	BM
Procurement	May be banked for rapid availablility	May be banked for rapid availablility
CFU fibroblasts	High concentration	The older the donor, the lower the concentration of CFU fibroblasts
Proliferation capacity	Higher proliferation capacity	Lower proliferation capacity, particularly with older donors
Expression of HLA class I and HLA-DR	Lower	Higher (potentially more immunogenic)
Concentration of MSCs	Higher	Lower
Treatment of GVHD	Effective and safe, potentially more advantageous	Effective and safe