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## Review Article

# Umbilical Cord-Derived Mesenchymal Stem Cells for Hematopoietic Stem Cell Transplantation

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Hematopoietic stem cell transplantation (HSCT) is becoming an effective therapeutic modality for a variety of diseases. Mesenchymal stem cells (MSCs) can be used to enhance hematopoietic engraftment, accelerate lymphocyte recovery, reduce the risk of graft failure, prevent and treat graft-versus-host disease, and repair tissue damage in patients receiving HSCT. Till now, most MSCs for human clinical application have been derived from bone marrow. However, acquiring bone-marrow-derived MSCs involves an invasive procedure. Umbilical cord is rich with MSCs. Compared to bone-marrow-derived MSCs, umbilical cord-derived MSCs (UCMSCs) are easier to obtain without harm to the donor and can proliferate faster. No severe adverse effects were noted in our previous clinical application of UCMSCs in HSCT. Accordingly, application of UCMSCs in humans appears to be feasible and safe. Further studies are warranted.

## 1. Introduction

Biologic interest in mesenchymal stem cells (MSCs), which were first described by Friedenstein and colleagues in 1966 [1], has risen dramatically over the last decade. As expected, clinical application of human MSCs is also evolving rapidly for a variety of diseases. Bone marrow (BM) remains a major source of MSCs in most investigations. Although umbilical cord (UC) rich with MSCs and UC-derived MSCs (UCMSCs) has been shown to be easy to isolate and culture, data available focusing on clinical application of UCMSCs are quite limited.

In this paper, we address the characteristics of MSCs, including UCMSCs, and their clinical application in hematopoietic stem cell transplantation (HSCT). We share our clinical experience in the successful use of in vitro expanded

UCMSCs [2–4]. We also describe several issues related to the clinical use of MSCs. For the near future, we anticipate that more patients can benefit from the therapeutic effects of UCMSCs.

## 2. Biologic Characteristics of MSCs

*2.1. The Definition of MSCs.* The defining characteristics of MSCs are inconsistent among investigators. According to the minimal criteria of the International Society for Cellular Therapy, MSCs are defined by their in vitro growth pattern, the expression of specific surface antigens, and the multipotent differentiation potential [5]. Being a member of stem cells, MSCs are able to self-renew with a high proliferative capacity. They proliferate as fibroblastic spindle-shaped cells and must be plastic-adherent when maintained in standard

culture conditions [5]. MSCs can be characterized by a panel of surface markers, which is negative for hematopoietic antigens (CD34, CD45, CD14, CD11b, CD19, and CD79 $\alpha$ ), and positive for mesenchymal makers (CD105 and CD73) and cell adhesion molecules (CD29, CD44, CD106, and CD90) [5–7]. MSCs display a broader differentiation potential, and the most unique property to identify MSCs is the capacity for trilineage mesenchymal differentiation, including osteoblasts, adipocytes, and chondroblasts [5].

**2.2. The Role of MSCs in Hematopoiesis.** MSCs play a critical role in providing the essential microenvironment for hematopoiesis. In BM, MSC-derived stromal cells establish an appropriate scaffold and a complex network of cytokines, adhesion molecules, and extracellular matrix proteins [8, 9]. In vitro, many studies have reported the promotive effects of MSCs for expansion of hematopoietic stem cells (HSCs) [10–12]. In animal models, MSCs have been shown to enhance engraftment of donor HSCs after cotransplantation [13–15]. Like BM-derived MSCs (BMMSCs), UCMSCs were demonstrated to support engraftment of a limited number of human HSCs from cord blood in a NOD/SCID transplant model [16].

**2.3. Immune Properties of MSCs.** MSCs express HLA-class I, but not class II [17, 18]. In vitro, several investigations have demonstrated that using mismatched MSCs does not trigger proliferative T-cell response in the allogeneic mixed lymphocyte reaction [12, 18, 19]. In vivo, transplanted allogeneic MSCs can be detected in recipients at extended time points, indicating a lack of immune recognition and clearance [20]. As for showing low immunogenic properties, it is convenient for the clinical application of MSCs.

MSCs possess immunomodulatory effects. Many studies have reported that MSCs can exert profound immunosuppressive effects via modulation of both cellular and innate immune pathways. MSCs suppress the proliferative response of B cells to allogeneic antigens through an arrest in the G<sub>0</sub>/G<sub>1</sub> phase of the cell cycle, and the major mechanism appears to be through soluble factors produced by MSCs [21–23]. MSCs also inhibit B-cell differentiation and affect their chemotactic properties [23]. Additionally, MSCs modify T-cell responses indirectly by blocking the differentiation of monocytes into dendritic cells and impairing the antigen-presenting ability [24]. MSCs also inhibit T-cell proliferation and function directly by secreting soluble factors [25–27]. Moreover, MSCs alter the cytokine secretion profiles of dendritic cells, T cells, and natural killer cells to induce a more anti-inflammatory or tolerant phenotype [20].

Taken together, MSCs are capable of escaping recognition by the alloreactive immune system and can exert immunomodulatory and anti-inflammatory effects. These properties make them a promising tool in the management of graft failure and in the prevention or treatment of graft-versus-host disease (GVHD) after HSCT.

### 3. Isolation of MSCs from Various Origins

MSCs are derived from mesodermal progenitor cells. They can be isolated from different tissues, including BM,

peripheral blood, adipose tissue, dental pulp, and a variety of fetal tissues, such as amniotic fluid, amniotic membrane, placenta, cord blood, and UC [7, 8, 17, 28–30]. A great impact on clinical utility is related to the abundance and isolation efficacy of MSCs from different sources. Though as a traditional source, MSCs constitute only a small percentage about one in  $3.4 \times 10^4$  cells in adult BM [31]. The frequency of MSCs in fetal tissues is likely to be higher [30]. However, MSCs are sparse in full-term infants' cord blood [31–33], whereas MSCs can be obtained and cultured much more efficiently from UC than from cord blood [34].

The ontological and anatomical origins of MSCs have profound influences on their properties, and hence affect their performance in clinical application. Many studies have found that MSCs derived from various origins share a similar spindle-shaped morphology and reveal a consistent immunophenotypic profile [6, 17, 30, 35]. Whereas compared with adult-type MSCs, fetal-type MSCs appear to have greater expansion capacity and faster doubling time which may result from their longer telomeres, greater telomerase activity, and higher expression of telomerase reverse transcriptase [6, 17, 28, 29, 36–38]. UCMSCs shares similar properties unique to fetal-type MSCs, and we and other authors also demonstrated the higher proliferative potential of UCMSCs [3, 39, 40].

Fetal-type MSCs are less lineage-committed [36] and express lower levels of HLA-class I than adult-type MSCs [6]. We found that the reduction in peripheral blood mononuclear cell proliferation activated by phytohemagglutinin stimulation was significantly greater in the UCMSC cocultures than in BMMSC cocultures, suggesting the greater immunosuppressive effects of UCMSCs [3]. Additionally, MSCs from various origins have heterogeneity in differentiation potential. For example, MSCs from UC or cord blood exhibit more robust osteogenic but less adipogenic differentiation than BMMSCs [6, 37, 39, 41].

### 4. The Superiority of UCMSCs in Clinical Application

BM is considered as a traditional source of MSCs, and most of the knowledge concerning MSCs comes from BM studies. However, several limitations restrict the clinical application of BMMSCs. Harvesting BMMSCs involves an invasive and painful procedure, which can cause infection, bleeding, and chronic pain. Additionally, BMMSCs exhibit accelerated senescence significantly with age [38].

On the contrary, UCMSCs are obtained after delivery of a baby from a sample that would be discarded inevitably. The process is noninvasive, painless, and harmless for the mother and the baby. UC contains a significant amount of MSCs which can be easily collected and cultured [34, 40]. In vitro, UCMSCs have greater expansion capability and faster growth rate [3, 17, 39, 40], indicating the advantage for rapid expansion and consequent downstream application.

UCMSCs express a lower level of HLA-class I than BMMSCs [40], suggesting the lower immunogenicity and the superiority for clinical use in HSCT. UCMSCs appear to

have greater immunosuppressive effects [3], indicating their better role in the management of GVHD. Therefore, UC represents a good alternative source of MSCs and should not be discarded as medical waste.

## 5. Clinical Application of MSCs in HSCT

*5.1. Promotion of Engraftment after HSCT.* MSCs are crucial for the specialized BM microenvironment. Chemotherapy and radiotherapy prior to HSCT damage the BM stroma, and may result in delayed engraftment. In 2000, Koç et al. first reported that coinfusion of autologous BMMSCs at the time of HSCT can lead to rapid hematopoietic recovery [42]. Accordingly, 46 patients received allogeneic HSCs and MSCs from HLA-identical siblings, and most patients had prompt hematopoietic recovery without significant side effects [43]. The beneficial effects of MSCs on engraftment may relate to their supportive role in hematopoiesis.

Bacigalupo et al. demonstrated that BMMSCs from patients with severe aplastic anemia were deficient in the ability to inhibit T-cell proliferation and cytokine release, indicating the lack of MSC immunoprotection in the BM [44]. We found that BMMSCs derived from children with severe aplastic anemia exhibit poor potential of proliferation and differentiation [45]. Due to the possibility of BMMSC insufficiency, we cotransplanted UCMSCs along with HSCs in 2 children with severe aplastic anemia [4]. Both achieved faster hematopoietic engraftment without infusion-related toxicities.

*5.2. Prevention and Treatment of Graft Failure.* Apart from engraftment promotion, MSCs were reported to be also efficient in prevention and treatment of graft failure. In 2007, Le Blanc et al. reported cotransplantation of BMMSCs with HSCs to prevent rejection in 3 patients with previous graft failure or rejection [46]. All the patients achieved hematopoietic engraftment and 100% donor chimerism, suggesting the potential role of MSCs in the management of graft failure. As T cell depleted HSCT from a HLA-haploidentical relative is a feasible option for the patient who needs to undergo allogeneic HSCT but lacks a HLA-compatible donor, the report of Ball et al. provides promising results [47]. While there was a graft failure rate of 15% in 47 historical control patients, no graft failure occurred among the 14 children receiving coinfusion of BMMSCs during haploidentical HSCT.

*5.3. Treatment of GVHD.* GVHD involves increased secretion of inflammatory cytokines, activation of a variety of immune cells, and finally host tissue damage. Severe GVHD after allogeneic HSCT has a high mortality rate. MSCs can modulate immune responses and lead to resolving of GVHD. In 2004, Le Blanc et al. first reported that a girl with acute lymphoblastic leukemia received infusion of haploidentical BMMSCs to treat severe treatment-resistant grade IV acute GVHD after HSCT, and the clinical response was striking [48]. Thereafter, eight patients with steroid-refractory grades III-IV GVHD were treated with expanded MSCs from HLA-identical or mismatched donors, and the survival rate was

significantly better than that of 16 comparable controls during the same period but not given MSCs [49]. In addition to the promising results of MSCs for GVHD, another important issue comes from their study: it is feasible and safe to use MSCs even from HLA-incompatible donors.

To date, clinical application of UCMSCs in the treatment of GVHD is very limited. According to our experience, we intravenously infused in vitro expanded UCMSCs four times into two recipients with severe steroid-resistant acute GVHD [3]. The clinical manifestations of GVHD dramatically improved after each UCMSC infusion, even without additional immunosuppressive therapies. Several studies demonstrated that MSCs of the donor can graft into the recipient's BM after allogeneic HSCT [43, 50, 51]. However, the marrow stroma remains host in origin after successful allogeneic HSCT [47, 52], suggesting that donor MSCs are eliminated in the recipient's BM after infusion. Therefore, more than one times of MSC infusion may be needed for patients with severe GVHD.

## 6. Issues Related to Clinical Application of MSCs

Because the number of MSCs obtained from the donor is not sufficient and MSCs have a great propensity for in vitro expansion, passaged cells are used extensively in experimental and clinical practice. Although karyotype analysis is not recommended for routine identification of MSCs, transforming events potentially leading to the establishment of a novel cell line may occur [5]. Additionally, MSCs may gradually lose their properties of early progenitor cells, including the abilities to proliferate and differentiate [53]. Thus, the conditions of MSC culture are very important for successful clinical use, and MSCs within six passages are suggested for clinical application [17].

MSCs may suppress host immunity against infectious agents, and it is uncertain whether viruses can be transmitted by MSCs from infected donors. Sundin et al. demonstrated that no viral DNA of cytomegalovirus, herpes simplex virus type 1 and type 2, Epstein-Barr virus and varicella zoster virus could be detected in MSCs isolated from healthy seropositive individuals [54]. Thus, the risk of herpes virus transmission is low when infusion of MSCs from healthy seropositive donors. However, cytopathological effects and intracellular viral antigens can be found after infection of cytomegalovirus and herpes simplex virus type 1 in vitro [54]. Therefore, MSCs may be susceptible in patients with viremia.

Coinfusion of in vitro expanded MSCs at the time of HSCT has been shown to be safe and feasible without immediate or late infusion-related toxicities [43, 47, 49], and patients given MSCs seem not to experience more infections [47]. However, the optimum MSC dose, the optimum number of infusions and the appropriate cell passages need to be further evaluated in large well-conducted clinical trials. In addition, UCMSCs are more primitive than BMMSCs. Although UCMSCs are easier to obtain without suffering to donors, the safety of these cells in human clinical application is still unclear due to the limited clinical experience. Besides, the quality of MSCs for human clinical use is crucial, but not

all physicians have facilities to guarantee the quality of cells. “Off-the-shelf” MSCs from MSC banks may make MSCs more available for clinical application.

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