

## Unique Features and Clinical Application Prospect of Human Umbilical Cord Mesenchymal Stem Cells

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### ABSTRACT

**AIM:** The purpose of the study was to summarize the unique features of human umbilical cord mesenchymal stem cells (hUC-MSCs) and their clinical application prospect.

**BACKGROUND:** It is well known that stem cells have great potential for self-renewal and multipotential differentiability. Over the past several years, extensive preclinical and clinical trials regarding cell-based therapy have been performed. Currently, mesenchymal stem cells (MSCs) from bone marrow have been commonly used as standard sources for cell-based therapies. However, there exist some disadvantages of bone marrow mesenchymal stem cells (BMSCs) as donor cells, include invasive isolate procedures, limited cell numbers and immune rejection. Therefore, the search for alternative MSCs sources is in urgent need.

**METHODS:** An electronic search in PubMed and OVID was undertaken in March 2016 using various combinations of the keywords 'human umbilical cord', 'mesenchymal stem cells' and 'therapeutic potential of human umbilical cord mesenchymal stem cells' during the period 1980 to 2016. The articles that are most relevant to our subject are selected. Moreover, we have hand-searched for additional relevant references that might pertain to hUC-MSCs.

**RESULTS:** Human umbilical cord ((hUC)) has recently been reported as an ideal substitute to bone marrow as a source of

MSCs. Moreover, MSCs harvested from hUC are pluripotent and immunologically naive. The morphology and biological characteristic of hUC-MSCs resembles that of MSCs isolated from bone marrow.

**CONCLUSION:** Cell-based therapy is an emerging field, which can offer great therapeutic potential in the complex human diseases. Compared with bone marrow, hUC has been considered as an ideal source of MSCs due to their little ethical obstacles, painless procedures involved, lower risk of immune rejection and convenient sources for autologous cell therapy. The rapid development of umbilical cord blood banks appears to provide plentiful supply of stem cells for regenerative medicine and tissue engineering.

**Key words:** Human umbilical cord; Mesenchymal stem cells; Hypoimmunogenic properties; Multipotential differentiation; Therapeutic potential of hUC-MSCs

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### INTRODUCTION

With the increasing prevalence and incidence rates in the complex human diseases, e.g., bone regeneration disease, cardiovascular disease, diabetic disease and hematopoietic disease, there exists an urgent need to search for more effective and efficient therapies. Cell-based therapy is a novel and potential therapeutic approach, which can replace diseased or damaged cells with minimal side effects by introducing stem cells to these tissues or organs<sup>[1-4]</sup>. Currently, BMSCs have represented the golden type of stem cell for cell-based therapies. Experimental and clinical studies have showed the self-renewal and multilineage differentiation capability of BMSCs<sup>[5-7]</sup>. However, it is quite difficult to produce large quantities of tissue/cells via bone marrow due to the decreasing frequency and differentiation potential with age. The harvesting of BMSCs also involves invasive procedures<sup>[8]</sup>. Therefore, the search for substitute of BMSCs is of

great value. Great interest have been given to the source of hUC, which is ethically acceptable and could provide abundant cells for cell-based therapy<sup>[9,10]</sup>.

Umbilical cords from consenting donors were collected after full-term caesarian sections. Not only hematopoietic stem cells (HSCs) but also MSCs can be harvested from hUC. And hUC-MSCs, originating from mesoderm, have been first reported by Eric A *et al* in 2000 (Figure 1)<sup>[11]</sup>. In addition, hUC-MSCs shared most of the features with MSC from bone marrow, including their morphology and biological characteristics<sup>[10]</sup>. A great quantity of evidence showed that hUC-MSCs have great potential for self-renewal and multipotential differentiation, which can be differentiated into osteogenic cells, adipogenic cells, neural cells, cartilage cells and others under specific induction of certain factors or stimulation<sup>[12-14]</sup>.

Compared with BMSCs, hUC-MSCs have more distinct advantages, such as accessibility, their little ethical constraints, painless and time-saved procedures involved, higher proliferation capacity, long term preservation, lower risk of immune rejection and viral contamination<sup>[14-18]</sup>. Moreover, numerous umbilical cord blood banks worldwide have been established to rapidly increase the supply of hUC-MSCs for cell-based therapy. Therefore, MSCs derived from hUC can be considered as new and promising substitute to BMSCs. Furthermore, hUC-MSCs can offer greater clinical utility in the field of regenerative medicine and tissue engineering. Here, we summarize unique features of hUC-MSCs and their potential clinical prospect.

## MATERIALS AND METHODS

An electronic search in PubMed and OVID was undertaken in March 2016 using various combinations of the keywords ‘human umbilical cord’, ‘mesenchymal stem cells’ and ‘therapeutic potential of human umbilical cord mesenchymal stem cells’ over the years 1980-2016. The period 1980 to 2016 was chosen because hUC-MSCs have been first reported by Eric A *et al* in 2000. And a growing number of investigations regarding hUC-MSCs have been conducted until now.

The articles that are most relevant to our subject are selected. Moreover, we have hand-searched for additional relevant references that might pertain to hUC-MSCs. The titles, abstracts (when available) and key words were read first for selecting relevant studies. These studies were then further identified via obtaining the full text. Eligibility criteria included studies reporting the latest information of hUC-MSCs with language restriction in English. Review articles without original data were excluded.

### Isolation and culture of hUC-MSCs

There are several methods to isolate MSCs from hUC, including plastic adherence, gradient centrifugation, flow cytometer and immunomagnetic beads<sup>[19]</sup>. Currently, the isolation of hUC-MSCs is commonly achieved by gradient centrifugation combined with plastic adherence. Briefly, mononuclear cells are collected by gradient centrifugation and cultured under specific and suitable medium (Figure 2). Based on respective time for different type of cells to attach into the same flask surface, rapidly-adherent cells (with characteristics of MSCs) can be obtained from these mononuclear cells. This commonly-used method is safe, simple, effective and cost-saving. However, the component of hUC-MSCs is complex<sup>[10,20]</sup>. Using flow cytometer, we can successfully isolate high-purified MSCs which expressed CD44, CD29, CD90 and others. Immunomagnetic beads can also be adopted to obtain high purity MSCs, which involve complicated procedures, high-demanding experimental condition and great risk of cell pollution<sup>[21]</sup>.

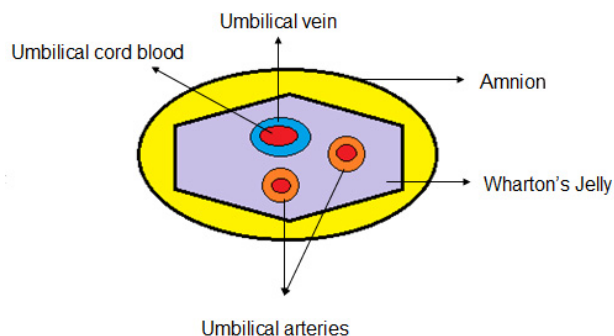


Figure 1 Illustration showing the cross-section of human umbilical cord.

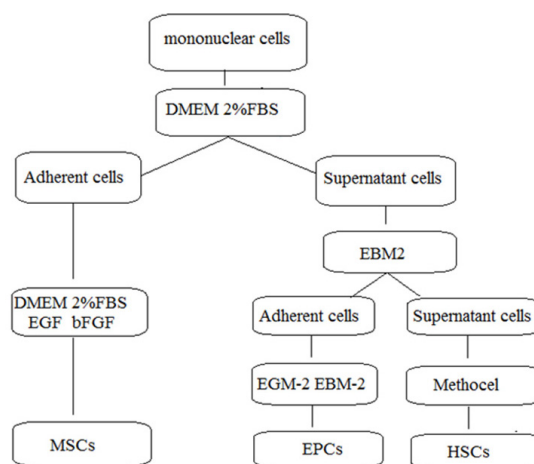


Figure 2 Flow chart demonstrating the main steps of derivation of stem cells from the human umbilical cord.

Concerning the cultivation of hUC-MSCs, there does not exist a unified and standard growth medium. Normally, they are incubated with Dulbecco's modified Eagle's medium (DMEM) or DMEM with low glucose (DMEM-LG). According to Cheng's studies, comparing two different growth medium, one is consisted of DMEM-LG and 2% fetal bovine serum (FBS), another DMEM-LG and 10% FBS, it concluded that cultivation in the growth medium with low level of FBS is benefit for keeping cell proliferation<sup>[22]</sup>.

### Morphology, immunophenotypic markers and proliferation patterns of hUC-MSCs

Fibroblastic-like cells from hUC can be observed after 4-5 days' initial plating. Moreover, their characteristics are similar to that of BMSCs, including fibroblastic morphology, immunophenotypic markers, growth characteristics, multi-lineage differentiation. However, hUC-MSCs have shown some unique features according previous reports. Firstly, hUC-MSCs showed lower expression of CD106 and HLA-DR in comparison with BM-MSCs, but were strongly positive for surface markers such as CD13, CD44, CD90, and CD166. This profile indicated hypoimmunogenic properties of hUC-MSCs favor for allogeneic cell-based therapy<sup>[13,20,23,24]</sup>. Secondly, the proliferation analysis showed strong proliferative ability of hUC-MSCs. Compared with BM-MSCs, hUC-MSCs reached a faster population doubling time and such proliferation characteristics kept for almost 30 passages<sup>[10,13,25]</sup>.

### Differentiation capacities of hUC-MSCs

A large body of investigations suggested that hUC-MSCs can be

differentiated into many demanded tissues. And large numbers of cells can be offered to replace the diseased tissues, such as bone, adipose, neuronal, endothelial and cardiomyocyte cells (Figure 3)<sup>[26]</sup>. When hUC-MSCs were treated with osteogenic induction, they differentiated into bone cells by detecting calcified matrix from UC samples. When hUC-MSCs were grown in adipogenic conditioned medium, they stained with oil red O and expressed lipoprotein lipase. When hUC-MSCs were treated with norm growth medium supplemented with acidic fibroblast growth factor (aFGF), sonic hedgehog (SHH), brain-derived growth factor (BDNF), nerve growth factor (NGF) and FBS and incubated at 37°C, 8% CO<sub>2</sub>, they were shown to differentiate into neurons. According to the research of Nishiyama N *et al*, it confirmed that hUC-MSCs can differentiate into cardiomyocyte cells using *in vitro* and *in vivo* models experiments<sup>[27]</sup>.

### Clinical application prospect of hUC-MSCs

Currently, gene therapy and tissue engineering have become very active areas of research in the medical field. Cell-based therapy can provide an innovative and effective approach for various human diseases. On the basis of recent studies *in vitro* and *in vivo*, hUC-MSCs have been considered as promising alternative sources for therapeutic intervention due to their unique primitive nature and capability of multipotent differentiation (Figure 3).

### Prospect of Bone repair and healing

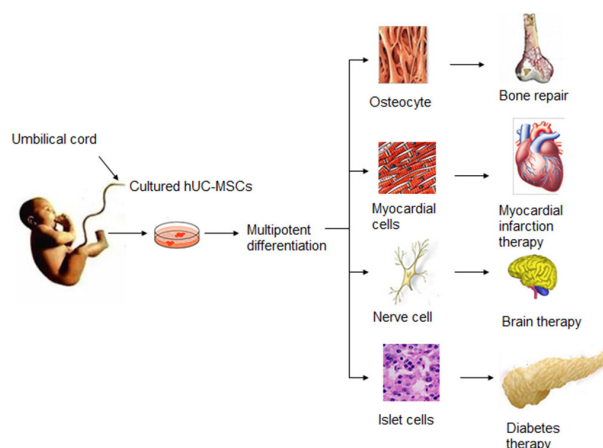
Osteogenesis imperfecta (OI) is characterized by osteopenia and bone fragility due to abnormal collagen production. Guillot PV *et al*, using a mouse model of OI, have demonstrated that there existed a clinically relevant reduction in incidence rate of bone fracture and huge improvement in the reparative bone tissue with the transplantation of hUC-MSCs<sup>[25]</sup>. In the stem cell transplantation groups, autologous hUC-MSCs had differentiated into bone cells and large numbers of new multi-center bone growth occurred, highlighting their therapeutic potential for bone repair and healing<sup>[14,21,28]</sup>.

### Prospect of diabetes therapy

Islet transplantation has been approved to be a potential treatment for either type1 or type2 diabetic patients. However, there exist some disadvantages of this effective method, including the limited number of donor islets and immune rejection. The increasing prevalent of diabetes and its long-term complication have presented a great challenge to search for more effective and safe therapeutic approaches. At present, hUC-MSCs appear to be a promising and safe cell source for transplantation due to their high potential for proliferation, multipotential differentiation and a low level of immunogenicity. According to the diabetic rats' models by Wang *et al*, hyperglycemia of the diabetic rats was corrected and the damage of pancreatic cells was partly repaired in the hUC-MSCs transplantation groups<sup>[29-31]</sup>.

### Prospect of myocardial infarction (MI) therapy

With the distinctive advantages of plentiful supply of pluripotent stem cells with a low level of immunogenicity and non-ethical constrain, the use of hUC-MSCs have been prompted great interest to treat MI in cell-based therapy<sup>[18,32,33]</sup>. According to previous reports, cardiac function after MI has been improved via intracoronary administration of stem cells from hUC due to promoted neovascularization and attenuation of cardiac remodeling<sup>[34]</sup>. Currently, the specific mechanisms of the beneficial effect of hUC-MSCs in MI are under investigation. Their potential effects may



**Figure 3** Differentiation capacities of hUC-MSCs and their clinical application prospect.

be caused by incorporating the delivered cells to the target tissue. Additionally, growing evidence has demonstrated the significance of their paracrine effect in providing cardioprotection. Extracellular membrane vesicles (MVs), secreted by different types of cells, have been considered important as tools of intercellular communication. MSC-released MVs contributed to the paracrine effects of stem cells via delivering intercellular information between stem cells and target cells and modulating immune responses<sup>[35-37]</sup>. Recent work by Lim's group has suggested that MSC-derived MVs played a great role in the protective effects on MI<sup>[38]</sup>.

### Prospect of brain ischemia therapy

Ischemic stroke have been ranked as the third cause of death in the US, which led to a serious threat to public health. Additionally, thrombolytic treatment and tissue plasminogen activator should be adopted within 3 h after stroke. The treatment involves limited therapeutic range, which have to be widened via more effective therapies. Numerous *in vitro* and *in vivo* models experiments have proved that hUC-MSCs transplantation can significantly improve patients' function and behavior via producing various neurotrophic factors and restoring the blood flow of infarcted area<sup>[39-41]</sup>. In the stem cell transplantation groups, autologous hUC-MSCs had differentiated into neuronal cells, characterizing their therapeutic potential for brain ischemia.

## CONCLUSION

In conclusion, a large body of preclinical and clinical trials over the past several years have demonstrated great therapeutic potential of stem cells in treating various human diseases. Compared with BMSCs, MSCs derived from hUC possess more distinct advantages, such as accessibility, their little ethical constraints, multipotent, higher proliferation capacity and lower risk of immune rejection. The clinical application prospect of hUC-MSCs cell-based therapy is promising in future. However, the fully realization of this potential will require further preclinical and clinical trials to confirm its validity and reliability.

## CONFLICT OF INTEREST

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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