

Potential Uses for Cord Blood Mesenchymal Stem Cells

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Abstract

Stem cell therapy is a powerful technique for the treatment of a number of diseases. Stem cells are derived from different tissue sources, the most important of which are the bone marrow (BM), umbilical cord (UC) blood and liver. Human UC mesenchymal stem cells (hUC-MSCs) are multipotent, non-hematopoietic stem cells that have the ability to self-renew and differentiate into other cells and tissues such as osteoblasts, adipocytes and chondroblasts. In a number of reports, human and mouse models of disease have hUC-MSCs treatments. In this article, we review studies that pertain to the use of hUC-MSCs as treatment for diseases.

Keywords: Cord Blood, Mesenchymal Stem Cells, Transplantation

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Introduction

Now a days, regenerative medicine in stem cell filed widely attractive by scientists. Stem cell therapy is a potential method for treatment of some disorders (1). Sources for stem cells vary, each of which have uses for certain diseases (2-4). Mesenchymal stem cells (MSCs) are one source for stem cells that are multipotent, non-hematopoietic and have the capability for self-renewal and differentiation (5, 6). MSCs can be isolated from bone marrow (BM), cord blood, placenta, adipose tissue and liver (2, 3, 7, 8).

According to the International Society for Cellular Therapy (ISCT), MSCs are distinguished by their abil-

ity: 1. adhere to plastic (when maintained in standard tissue culture flasks these cells should adhere to the bottom of the flask); 2. express specific surface antigens (>95% of these cells, express CD73, CD90 and CD105 and are negative for CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA-II); and 3. under standard differentiating conditions *in vitro* they have the capability to differentiate into osteoblasts, adipocytes and chondroblasts (Table 1, Fig 1) (9). In addition, MSCs should have the capability to differentiate into endothelial, epithelial, hepatocytes and neural cells (10-14). Other properties of MSCs include ease of separation, immunomodulatory effects, migratory behavior and no ethical limitations (15).

Table 1: Summary of criteria for the identification of MSCs (9)

1 Adherence to plastic under standard culture conditions	Positive (≥95% +)	Negative (≤2% +)
2 Phenotype	CD105	CD45
	CD73	CD34
	CD90	CD14 or CD11b
		CD79α or CD19
		HLA-DR
3 In vitro differentiation: into osteoblasts, adipocytes, and chondroblasts		

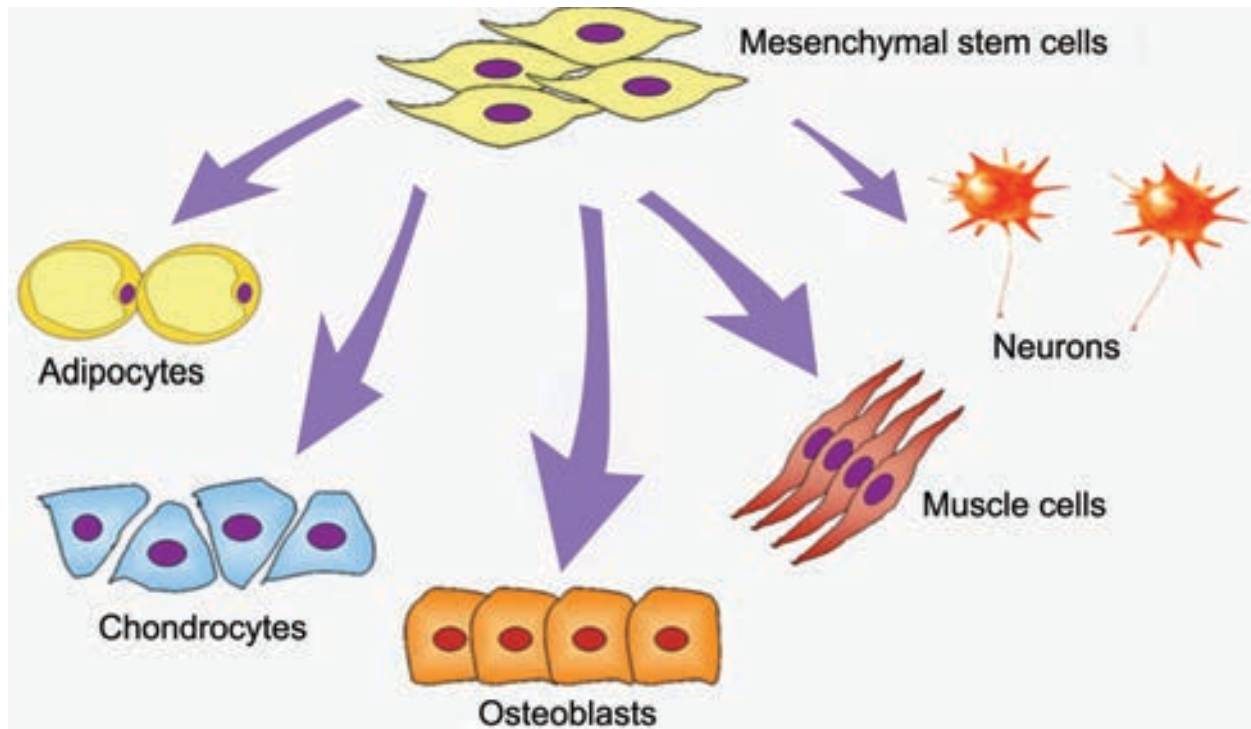


Fig 1: Differentiation potential of MSCs (26).

In addition to BM, the human umbilical cord (UC) is an alternative source for MSCs (16, 17). UC-MSCs for stem cell therapy have advantages over BM-MSCs because they are easily available, collection from the donor is neither invasive nor painful, and there are no ethical considerations (18). UC-MSCs are more primitive than BM-MSCs and have the capability to differentiate into different cells (19-22). In addition to the previously mentioned CD markers, they also express CD29, CD44, CD49b, CD58, CD166 and HLA-I. They are negative for CD3, CD7, CD33, CD40, CD49d, CD80, CD86, CD117, and CD133 (23-25).

The current review discusses pre-clinical and clinical human umbilical cord mesenchymal stem cell (hUC-MSCs) application in the treatment of some disorders.

Regenerative medicine

Regenerative medicine is the process by which

human cells and tissues are used to restore normal function. In this field, MSCs have the capability to differentiate into multiple cell lineages such as osteoblasts, chondrocytes and adipocytes.

Neurological disorders

Cerebral ischemia

Cerebral ischemia, also known as brain ischemia, results from a lack of blood flow to the brain that leads to cerebral hypoxia and results in neurological injury. This condition results in major complications such as impairments in vision, physical movement, and speech. If the appropriate diagnosis and treatment are not performed, symptoms may be permanent and life-threatening. Neurological recovery following stem cell transplantation in animal model with ischemia has shown the safety and effectiveness of this type of transplantation (27). Several studies have reported in general that hUC-MSC transplantation into the cortex of

an occluded middle cerebral artery can result in the successful recovery of neurological function in a mice model (28). In this process have been shown that hUC-MSCs migrate to the ischemic area and differentiate into neurons, glial and other different types of neural cells. There appears to be increased cortical blood flow in the ischemic zone because of angiogenesis by hUC-MSCs. Koh et al. (29) have shown recovery of neurobehavioral function and decreased infarct volume after transplantation by hUC-MSCs. This group of researchers has shown that the neuroprotective effect of hUC-MSCs caused an improvement in behavioral function. According to other study hUC-MSCs transplantation significantly reduced the injury mass and deficiency of neurological function due to angiogenesis in a rat model of ischemic cerebral injury (30).

Spinal cord injury

Spinal cord injury (SCI) that arises from damage or trauma to the spinal cord because of loss or disturbed function results in reduced mobility (31). Yang et al. (32) have recently published impressive data that hUC-MSC transplantation can be a potential strategy for the promotion of corticospinal fiber regeneration and improvement in locomotor function following spinal cord transection into the lesion area of SCI rats compared with a control group. The results showed increased numbers of regenerated axons in the corticospinal area of the zone around the SCI lesion. Migration of hUC-MSCs from the implantation zone was observed. This group of researchers hypothesized that the release of cytokines and growth factors from stem cells was the key mechanism for corticospinal fiber progression.

Parkinson disease

Parkinson disease (PD) is a neurodegenerative disorder defined by progressive loss of striatal dopaminergic function (33). Fu et al. (34) have reported in a PD rat model with an infusion of hUC-MSC into the striatum resulted in a partial improvement the lesion-induced amphetamine-evoked rotation. In another study, Weiss et al. (35) found the same

results in a hemiparkinsonian rat model.

Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by loss of neurons and synapses in the cerebral cortex, dementia and histopathological symptoms such as senile plaques and neurofibrillary tangles (36). A deposit of amyloid- β peptide ($A\beta$) in the brain is the fundamental cause of this disease (37). In addition, oxidative stress and inflammatory effects may have a pathological role in AD. AD is progressive and to date, incurable (38-40). There are some evidences for the efficacy of cell therapy in AD. Lee et al. (41) have shown that use of hUC-MSCs in cell culture medium and an AD mouse model can reduce and ameliorate disease symptoms. This group has reported that co-culture of hUC-MSCs with hippocampal neurons resulted in a significant reduction in apoptosis compared with the control group. Also they have shown that injection of $A\beta$ in the brain of a mice model that transplanted hUC-MSCs led to diminished oxidative stress and glial activation compared with the control group. Stephan et al. (42) and Tsai et al. (43) reported that hUC-MSCs suppressed activated astrocytes and microglia activation which increased in the test group. According to this data, they have suggested that hUC-MSCs cells may have a neuroprotective role. Learning and memory can be improved by administration of hUC-MSCs in an acute AD mice model.

Support of hematopoiesis

MSCs have the potential capacity to support hematopoietic stem cell growth both *in vivo* and *in vitro* (44, 45). The main mechanism of hematopoiesis involves secretion of a number of major hematopoietic cytokines such as IL-6, IL-7, IL-8, IL-11, IL-14, IL-15, M-CSF and SCF (20). In a study by Bakhshi et al. (46), it was shown that hUC-MSCs could support the growth of CD34⁺ cord blood cells as determined by long-term culture initiation cell culture (LTC-IC). In another study, researchers have shown that UC-MSC compared with BM had

the capability to produce hematopoietic growth factors such as IL-6, IL-8, IL-11, G-CSF, GM-CSF and LIF (25). Researchers show that hUC-MSC increases homing and migration of UCB CD34⁺ cells to the BM and spleen. According to evidence, there is low efficacy of UC-MSC hematopoietic support capacity compared with BM however UC-MSCs have the ability to support long-term hematopoiesis *in vitro* (47).

Autoimmune diseases

Immunomodulatory effects of MSC have a critical role in the mechanism of autoimmune diseases. MSCs express low levels of HLA-I, but do not express HLA-II co-stimulatory molecules such as CD80, CD86 and CD40. In addition, these cells suppress activated T-cell proliferation and differentiation (48).

Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) or juvenile diabetes is an autoimmune disease of insulin-producing beta cells of the pancreas (49, 50). Although this disease can occur in any age group, it is mostly diagnosed in children and young adults. Common methods for controlling T1DM are insulin injections and self-monitoring blood glucose levels. Islet transplantation is the most efficient medication for patients diagnosed with insulin-dependent diabetes. Some studies have shown the application of different kinds of stem cells (embryonic, pancreatic, hepatic, BM and UC blood) in insulin production (51-56). Researchers have produced islet-like cells *in vitro* from hUC-MSCs which were then infused into the livers of diabetic rats. After transplantation, these cells secreted human C-peptide and in response to physiological glucose levels, released human insulin.

Advantages such as availability, large donor pool, non-invasive to the donor and low risk of rejection exist for using transplanted hUC-MSCs (47, 57). Limitations exist for UC, BM and ESC such as the low amount of UC, limited expansion and differentiation of BM, and ethical issues with the use of ESCs. Therefore transplantation of hUC-MSCs is the most efficient method for treating T1DM (58).

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that can affect any part of the body. SLE occurs more often in women than men (59). This disease may be the result of an attack by the immune system on cells and tissues of the body that occurs by producing antibodies against itself. SLE most often causes damage to the heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system. In a research study, Sun et al. (60) chose patients with severe SLE refractory to conventional immunosuppressive or immunomodulatory therapy (glucocorticoids, cyclophosphamide and mycophenolate mofetil) to receive hUC-MSCs. Following transplantation, patients were evaluated according to the SLE disease activity index (SLEDAI) which assessed anti-nuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA) antibody, levels of serum complement C3, C4 and albumin, and renal function (60). After a period of one month, SLEDAI scores significantly decreased in all 16 patients. The results of this study stated that additional decreases in SLEDAI were observed after three and six months. At three months following hUC-MSC transplantation, levels for 24-hour proteinuria, serum creatinine and urea nitrogen were measured for assessment of renal function. All of these parameters decreased and additionally, serum albumin returned to normal levels. As an indicator of immune system response, the researchers evaluated Treg cells (CD4⁺ FoxP3⁺ T cells). The results showed increased numbers of Treg cells and the ratio of Th1 and Th2 re-established after UC-MSCT. It postulated that an immune mechanism played a key role in the response to a successful engraftment (60).

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that involves 1% of the world's population and most frequently occurs in women. This disease affects numerous tissues and organs, but the synovial joints are the major target (61). The most common adverse effects of RA are destruction of artic-

ular cartilage and ankylosis of the joints (62). Proinflammatory cytokines such as TNF- α , IL-6, IL-1 β and IL-17 have an important role in pathogenesis of RA (63). There is no known cure, however treatment can lessen symptoms. New therapeutic agents such as TNF- α and B cell depleting therapy exist, however they are expensive and not usually used (64). Today, UC-MSCT is a new therapeutic method for treatment of RA. Liu et al. (63) by co-culturing UC-MSCs with synovial tissue harvested from patients with RA, have shown that UC-MSCT inhibited fibroblast-like synoviocytes (FLSs). FLSs, are resident cells of synovial joints that have a crucial role in inflammation and joint destruction. UC-MSCs suppressed the invasive behavior, MMP-9 expression and inflammatory response of FLSs. In addition, Treg cells that play an important role in maintenance of self-immune tolerance in RA significantly increased. Assessment of UC-MSCT on collagen-induced arthritis (CIA) in a mouse model explored that these cells prevented tissue damage, reduced inflammatory responses and Re-established the ratio between Th1 and Th2 cells. The results showed that, UC-MSCT significantly improved CIA in mice.

Wound healing

Delay and lack of skin reconstitution, infection, decreased circulation, low nutrition and low numbers of stem cells are common problems in persons with deep wounds (65). In a study of a mice model with a full skin defect, injection of hUC-MSCTs in the wound site has shown significantly enhanced wound healing with a much thicker newly formed epidermis layer in the experimental group compared with the control group (66). A significant increase in the amount of cells was observed in the regenerated skin tissue with improved dermal ridges. In the experimental group, folliculus pili and other appendixes had an important role in repairing skin tissue which was not observed in the control group. UC-MSCT caused more rapid, enhanced and improved wound healing.

Conclusion

Various methods exist as treatment for different diseases. One of the newest methods in regenerative medicine is stem cell therapy. Because stem cells have special advantages such as the ability to self-renew and differentiate into different cells and tissues, these cells are appropriate sources as treatment for several disorders. In addition to BM, the UC is a rich source of MSCs. MSCs are a source of stem cells that have potential power to improve responses to diseases such as T1DM, cerebral ischemia, SCI, PD, SLE and RA. There are potential advantages such as the profound immunomodulatory effects in the application of MSCs as treatment for different disorders.

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