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REVIEW PAPER

Stem cells for reprogramming: could hUMSCs be a better choice?

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Abstract Human umbilical cord mesenchymal stem cells (hUMSC) are primitive multipotent cells capable of differentiating into cells of different lineages. They can be an alternative source of pluripotent cells since they are ethically and regulatory approved, are easily obtained and have low immunogenicity compared to embryonic stem cells which are dogged with numerous controversies. hUMSC can be a great source for cell and transplantation therapy.

Keywords Human umbilical cord mesenchymal stem cells · Embryonic stem cells · Pluripotency · Reprogramming

Introduction

Reprogramming refers to the reversal of a mature differentiated cell type to a less differentiated one or the conversion of a differentiated cell type into another as depicted in the generation of embryonic stem cells (ESCs) from neurons by somatic cell nuclear transfer (SCNT) and the conversion of a B-lymphocyte to a macrophage (Eggan et al. 2004; Xie et al. 2004).

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Since the successful creation of "dolly" the sheep from an adult mammary gland cell (Wilmut et al. 1997), increased interest has been observed in the field of reprogramming, with numerous studies trying to produce pluripotent cells from different cell types (Aasen et al. 2008; Tsai et al. 2010; Li et al. 2009; Cai et al. 2010).

The importance of reprogramming cannot be understated since the cells generated hold promise for use in transplantation therapy, drug screening, patient specific disease models and as a basis for understanding developmental processes.

The zygote, formed during fertilization, is considered totipotent and as such able to differentiate into all cell types of an organism. On the other hand, ESCs derived from the inner cell mass (ICM) of the blastocyst (Thomson et al. 1998) are pluripotent with the ability to differentiate into the three germ layers (Chambers and Tomlison 2009). A number of adult stem cells such as mesenchymal stem cells and hematopoietic stem cells are multipotent and mainly differentiate into cells of their respective lineage (Konrad and Kathrin 2009).

Pluripotency can further be described as that ability of a cell to give rise to all cells of an embryo and adult with the exception of self organization in generating a whole organism (Solter 2006; Niwa 2007).

This property is transient during embryonic development and is observed in the cells of the ICM of the blastocyst, epiblast and maintained in the primordial germ lineage. Pluripotency is governed by a close

relationship of a set of transcription factors; Oct-4, Nanog and Sox2 whose levels are critical in the maintenance of the undifferentiated state (Chambers and Tomlison 2009; Niwa 2007).

Most reprogramming studies carried out involve the use of mature adult cells which have been associated with lower efficiency rates. Kato et al. (2000) observed that fetal and newborn skin and liver cells were better reprogrammed through SCNT compared to adult derived cells. Clones developed from adult cells expressed higher rates of abnormalities compared to their newborn or fetal derived counterparts. A similar effect is seen with induced pluripotent stem cells (IPS) where different cells can be reprogrammed with varying efficiencies (Li et al. 2009). These studies clearly illustrate that cells not fully matured or those expressing some degree of pluripotency or multipotency would provide better sources for reprogramming compared to their mature counterparts.

ESCs are pluripotent and would be a great source of cells for cell therapy. Unfortunately, their use has been hampered by ethical and regulatory hurdles; necessitating the search for alternative cells. Mesenchymal stem cells are multipotent adherent fibroblastic cells capable of differentiating into multiple mesenchymal lineages and other tissue cell types (Seung et al. 2005). They can also be greatly expanded ex vivo and are able to migrate to the sites of injury, inflammation, tumors (Chen et al. 2008) and are less immunogenic compared to ESCs. They may therefore be considered as alternatives to ESCs in transplantation therapy and reprogramming since their use is not hampered by ethical and regulatory debates as in the case of ESCs.

This review discusses various stem cells, such as, ESCs, hematopoietic stem cells, human umbilical cord mesenchymal stem cells (hUMSC), and looks at the benefits and challenges encountered with their use. Moreover, it proposes the use of mesenchymal stem cells obtained from the umbilical cord for cell therapy and reprogramming due to their ease of availability and absence of the regulatory hurdles associated with ESCs.

Embryonic stem cells (ESCs)

ESCs are derived from the ICM of the blastocyst stage embryo and have the properties of pluripotency and self renewal (Thomson et al. 1998; Martin 1981). They are further characterized by the expression of specific surface markers such as stage-specific embryonic antigens (SSEA) 3 and 4 in humans, SSEA 1 in mice, tumor rejection antigen-1–60 (TRA-1–60) and TRA-1–81 as well as germ cell tumor marker-2 (GCTM-2), alkaline phosphatase and high telomerase activity (Findikli et al. 2006). Specific culture conditions are required to maintain their undifferentiated state. Furthermore their ability to differentiate into various tissues and self renewal has been shown to be under the control of certain genes such as Oct4, Nanog and Sox2 which work in a regulatory circuit (Niwa 2007). ESCs spontaneously differentiate into cells of the three germ layers when injected into immunocompromised mice by forming teratoma and embryoid bodies in suspension cultures (Itzkovitz-Eldor et al. 2000; Przyboski 2005). Moreover, the differentiation of ESCs into neurons, cardiomyocytes, hepatocyte like cells and others has been achieved (Blum and Benvenisty 2005). More studies are underway to establish ESCs based therapies especially in heart failure, neurodegenerative diseases and diabetes.

ESCs seem to be the best choice in transplantation therapy since they are readily pluripotent and can be genetically manipulated. In fact reprogramming studies have always tried to achieve the various characteristics exhibited by ESCs using adult and fetal cell types. However, the use of ESCs is associated with technical, clinical and regulatory challenges.

The acquisition of ESCs from sources such as discarded embryos from IVF, therapeutic cloning and others has elicited moral and ethical questions since there is an ultimate destruction of the embryo, considered the beginning of human life by some (Suaudeau 2011). Although countries such as UK and Finland have legalized the use of embryos for research, others still have stringent regulations thus hampering the use of human ESCs for research. It is on this note that other alternatives to ESCs are hotly being pursued.

The use of feeder cells for the maintenance of ESCs undifferentiated state in culture poses great challenges in regard to large scale production and clinical application. Although alternatives to feeder cells are still being pursued, the introduction of xenogeneic material still poses great risk for therapeutic application (Findikli et al. 2006).

Successful transplantation of organs and tissues is often hampered by immune responses and graft rejection accruing from donor and recipient mismatch. Although some studies show that undifferentiated human ESC express low levels of MHC class I antigen, lack MHC class II and co-stimulatory molecules and can induce immunotolerance and immunomodulation in immunocompetent mice, others have revealed their immunogenicity especially in ongoing inflammation (Micha and Nissim 2004; Buja and Vela 2010). Moreover differentiated derivatives of human ESCs demonstrate an up regulation of MHC antigens (Drukker et al. 2002). Although the use of ESCs provides a better alternative to somatic cells in transplantation, there is need for more conclusive studies pertaining to their immunogenicity before meaningful clinical application is achieved.

Previously, human ESCs were thought to be karyotypical stable in prolonged in vitro cultures. However this seems unlikely since trisomies were detected for chromosomes 12 and 17 and attributed to the number and passaging technique used (Brimble et al. 2004; Draper et al. 2004). Of note is the formation of teratoma by ESC when injected into immunodeficient mice. Although it is considered a marker of human ESC pluripotency, it is of great concern therapeutically. Culture adapted human ESC were found to form less mature tumors compared to their non adapted counterparts, while the transplantation of ESC resulted in cardiac teratomas in immunodeficient animals (Buja and Vela 2010; Blum and Benvenisty 2008). In as much as strategies such as transplanting into immunopriviledged sites have eliminated teratoma formation, great care still needs to be observed in order to ensure the safety of ESCs use.

It is against these backgrounds that other pluripotent cells are currently under intense investigations in order to circumvent the limitations posed by the use of ESCs. Of these, mesenchymal stem cells especially hUMSCs which are easily obtained together with IPS seem to hold great promise in reprogramming and transplantation studies.

Haematopoietic stem cells (HSC)

HSCs are the best characterized of all adult stem cells, are rare with a frequency of 1 in 10,000 to 100,000 total blood cell (Fumio and Toshio 2007) and are multipotent with an ability to produce various blood cell lineages. They can be identified by different surface markers most commonly CD34, c-kit, lin-, although recent studies have revealed the presence of CD 34^- HSCs. Their origin has been controversial but have been suggested to arise from the haemogenic endothelium of the ventral wall of the dorsal aorta (Wilson et al. 2007) with an initial appearance in the yolk sac at about 6 weeks of gestation in humans and 10 days in mice (Zon 2008), followed by appearance in the aorta-gonadal mesonephros region, placenta, the fetal liver and finally the bone marrow (Huang et al. 2007; Kobayashi et al. 2010).

Their ability for self renewal and differentiation was first identified by Till, Siminovitch and McCullough (Till and Mcculloch 1961; Till et al. 1963) who through a series of experiments demonstrated their ability to reconstitute hematopoiesis in lethally irradiated mice. Of all the HSCs found during embryogenesis only those from the yolk sac do not self renew.

Based on their renewal ability, they can be classified into long term and short term reconstituting HSCs. Long term reconstituting HSCs, possess a greater renewal capacity and can maintain lifelong haematopoiesis in vivo (Luis et al. 2009; Blank et al. 2008). Self renewal of HSCs is controlled by both the intrinsic and extrinsic regulatory systems with a host of transcription factors and signaling pathways having been documented to influence self renewal. The homeobox {HOX} transcription factors are essential since they control the self renewal, proliferation and differentiation of haemopoietic stem cells (Kobayashi et al. 2010; Fortunel et al. 1998).

HSCs exhibit different properties depending on their location. The fetal liver and the bone marrow are the main organs involved in their expansion and differentiation. In the fetal liver they undergo rapid division while those in the bone marrow are quiescent and rapidly divide in case of blood loss or injury. In the bone marrow, quiescent cells are located in the endosteal niche while regeneration and replacement occurs in the vascular niche. Osteoblasts, mainly seen in the endosteal niche, regulate HSCs through secretion of signaling molecules and expression of cell adhesion molecules and as such are mainly associated with primitive HSCs. On the other hand, differentiating HSCs are found in the vascular niche characterized by different cell types such as endothelial and CXCL12-abundant reticular (CAR) cells. Although

the influence of osteoblasts on HSCs is irrefutable the exact molecular mechanisms are not well elucidated (Martin and Roger 2010; Wu et al. 2009; Michael et al. 2008; Jung et al. 2008; Magnusson et al. 2007).

Since current reprogramming studies have mainly focused on cells other than HSCs, it is important to note that these cells have been very instrumental in medicine especially in the treatment of hematopoietic malignant diseases, inherited blood disorders and as such have long been in clinical use. Recently, HSCs have been applied in reduced intensity conditioning (RIC) regimens for the treatment of recurrent malignancies especially in older patients. Although RIC treatment provides lower incidences and severity of acute graft versus host disease (GVHD) compared to myeloablative regimens, cases of late GVHD have been experienced (Servais et al. 2011). In addition, their potential benefits in treating autoimmune diseases such as therapy resistant rheumatoid arthritis and multiple sclerosis has been explored even though the risk of GVHD is still a concern (Sykes and Nikolic 2005). In this regard the use of hUMSCs could provide a better alternative to HSCs since they have been found to be immunomodulatory and their transplantation does not elicit immune reactions (Herrero and Pérez-Simón 2010).

Although previous reports indicated the rarity of HSC "transdifferentiation" or "plasticity" (Wagers et al. 2002) recent studies show the converse. In a mouse model of osteogenesis imperfecta, transplantation of 50 bone marrow cells highly enriched for HSC, greatly improved the bone volume and trabecular thickness suggesting the generation of bone cells (Mehrotra et al. 2010). The regeneration of hepatocytes in a female FAH $^{-/-}$ mouse model by the transplantation of purified HSCs derived from male ROSA26/129SvJ mice, has also been demonstrated (Lagasse et al. 2000). The above reports and others not documented here reveal a greater possibility in the use of HSCs especially in the field of tissue replacement in cases of trauma or injury, an area not fully explored using HSCs.

In as much as the benefits are numerous, HSCs transplantation has been hampered by various limitations, most common being GVHD in recipients specifically in allogeneic transplantation. On the other hand, disease relapse has also been cited as issue in some cases. Although interventions such as a second HSC transplant and donor lymphocytes infusion can be applied the former is associated with high morbidity rates while the latter with GVHD (Dazzi and Fozza 2007). Moreover the rarity of HSCs be it from the bone marrow or peripheral blood may hinder its use since transplantation requires use of a large number of cells and that obtaining HSC from the marrow is in itself an invasive and painful procedure.

It is therefore important to find alternative cells that can overcome these limitations in transplantation as well as regenerative medicine. To this end mesenchymal stem cells seem more promising since they overcome some of the above mentioned limitations.

Umbilical cord blood mesenchymal stem cells (UCB-MSC)

Although cord blood is a well documented source of hematopoietic stem cells, the presence of mesenchymal stem cells has been controversial. Initial studies on isolation suggested an absence of mesenchymal stem cells in cord blood (Mareschi et al. 2001; Gutierrez- Rodriguez et al. 2000) while subsequent studies confirmed existence and differentiation potential (Erices et al. 2000; Lu et al. 2010; Chang et al. 2006a). In a comparative study of adipose tissue, bone marrow and cord blood mesenchymal stem cells, 100 % isolation rate was achieved for bone marrow and adipose tissue MSC while only 63 % was seen with cord blood. Further, the frequency of colony formation was lowest with cord blood cells. Despite this, cord blood cells still proved to have the highest expansion capacity in vitro (Kern et al. 2006). A number of studies have demonstrated the ability of cord blood MSC to differentiate into chondrogenic and osteogenic lineages in appropriate conditions; although conflicting reports exist regarding adipogenic differentiation (Chang et al. 2006b; Kern et al. 2006; Kang et al. 2006; Chang et al. 2006a). Two different morphologic phenotypes have been isolated from cord blood mesenchymal progenitor cells (MPC). The spindle shaped MPC demonstrated a higher sensitivity towards adipogenic differentiation compared to the flattened MPC. Furthermore the former expressed higher levels of CD 90 compared to the latter (Chang et al. 2006a). The existence of the two different phenotypes can therefore explain the disparities in adipogenic differentiation as reported by separate groups.

Umbilical cord blood mesenchymal stem cells can further be differentiated into cells of the ectodermal and endodermal lineages such as neurons, hepatocytes and cardiomyocytes (Kang et al. 2006; Nishiyama et al. 2007). Transplantation into a mouse model of acute Alzheimer's disease revealed a reduction in oxidative stress, glial activation and apoptosis (Lee et al. 2010), moreover transplantation in a rat model of liver cirrhosis inhibited the expression of TGF-β 1, collagen type 1, and α-SMA (Kim et al. 2010). In an acute Kidney injury mouse model, UCB-MSC transplantation improved renal function, tubular cell injury and prolonged survival (Morigi et al. 2010). UCB-MSC can also inhibit the proliferation of MDA-MB-231 cancer cells by secreting dickkopf1 and hence suppressing the canonical WNT signaling pathway. They were also able to prevent metastases by up regulating PTEN in cancer cells (Sun et al. 2010). Treatment of patients with Buerger's disease relieved ischemic rest pain and healed necrotic skin lesions within 4 weeks of treatment (Kim et al. 2006). These experiments indicate the potential of cord blood cells not only in the treatment of degenerative central nervous system diseases but also in the event of acute injuries where they promote regeneration and healing. More clinical studies need to be undertaken in order to translate these results into clinical benefits. UCB-MSC express surface antigens such as CD73, CD105, CD44, CD 166 and MHC class I but lack MHC class II and co-stimulatory molecules such as CD80, CD86, CD40, mainly expressed in antigen presenting cells (Wang et al. 2009). Successful transplantation of UCB-MSC has been attributed to their immunosuppressant and immunomodulatory effects through the inhibition of lymphocyte proliferation, immunostimulatory cytokines such as tissue necrosis factor alpha (TNF-A), interferon gamma (IFN-Y) and inhibition of mature dendritic cells activity via cell to cell contact and secretion of soluble factors as seen in in vitro studies (Wang et al. 2009; Oh et al. 2008).

The cryopreservation of UCB-MSC had no effect on their characteristics as mesenchymal stem cells in terms of morphology, proliferation and differentiation potential. A viability of 90 % was obtained on thawing (Lee et al. 2004). This proves that long term storage for future applications is feasible.

The immaturity of UCB-MSC compared to other adult MSCs, makes it a better cell choice for cell therapy and reprogramming. The Pluripotency marker, Oct-4 was also seen in about 73 % of UCB-MSC. Its inhibition with lenti-viral vector-based small hairpin RNA (shRNA) resulted into growth retardation and repressed adipogenic differentiation (Seo et al. 2009).

Umbilical cord blood mesenchymal stem cells have an advantage over bone marrow derived MSC's since they can be obtained by non invasive methods (Rubinstein et al. 1993).

As earlier stated, umbilical cord blood has traditionally been a source of HSCs and not MSCs. Although cord blood provides some MSCs the harvest rate is known to be much lower compared to the umbilical cord and hence hUMSCs may be obtained in greater numbers at any particular time compared to UCB-MSCs.

Human umbilical cord mesenchymal stem cells (hUMSC)

The umbilical cord is composed of two arteries and one vein surrounded by a connective tissue stroma rich in mucopolysaccharidase and proteoglycans (Sobolewski et al. 1997) referred to as the Wharton's jelly.

Mesenchymal cells have been isolated from the umbilical cord arteries,vein including the sub-endothelial, perivascular areas, the Wharton's jelly (Ishige et al. 2009; Yuri et al. 2003; Sarugaser et al. 2005) and are characterized by the expression of CD29, CD10, CD44, CD90, CD13, SH2 and HLA-ABC with a lack of CD 34, CD45, CD31, CD38, CD14 and HLA-DR. Their expression levels of SH2 and HLA-ABC were lower than in bone marrow derived mesenchymal cells suggesting a more primitive population (Weiss et al. 2006; Lu et al. 2006). Various studies have documented their multipotency arising from their ability to undergo osteogenic, chondrogenic and adipogenic differentiation in specified conditions (Lu et al. 2006; Karahuseyinoglu et al. 2007). A variation in the ability to differentiate into the aforementioned lineages was noted between cells derived from the arteries, veins and Wharton's jelly. Cells from the Wharton's jelly had a lower affinity for osteogenic differentiation compared to the others (Sobolewski et al. 1997). Furthermore their multipotency has been demonstrated by differentiation into neurons, cardiomyocytes, hepatocyte like cells, oligondendrocytes, and insulin producing cells (Chao et al. 2008; Wang et al.

2004; Zhang et al. 2009, 2010; Ma et al. 2005). Their multipotency is essential since the resulting cells can be applied in replacement therapy in their differentiated or undifferentiated forms. Differentiation into neurons would serve a great purpose in the treatment of stroke and other neurodegenerative diseases which currently rely heavily on management and maintenance therapies. Likewise the treatment of diabetes and heart diseases would greatly benefit from the use of hUMSCs for replacement therapy.

The potential for use of hUMSC in transplantation medicine has further been revealed from successful transplantation studies in animal disease models. In a study by Cao et al. (2010) the use of hUMSC in ischemia/reperfusion induced acute renal failure in rats, resulted in increased levels of proliferating cell nuclear antigen (PCNA) with a decrease in caspace-3, IL-1b, IL-6 and TNF-a, indicating the promotion of renal cell proliferation and decreased apoptosis and inflammation.

Fu et al. (2006) reported a partial improvement of lesions in a rat parkinsonian disease model from transplantation of dopaminergic neurons derived from induced hUMSC. Treatment of type I diabetes with cells differentiated from hUMSC was demonstrated in a study by Chao et al. (2008). In addition, transplantation of hepatocyte-like cells obtained from hUMSC into CCl4-induced liver injury mouse model promoted recovery and indicated low rejection from the host (Zhao et al. 2009; Yan et al. 2009).

Transplant rejection and GVHD are major hindrances to cell therapy. Mesenchymal stem cells inhibit immune responses from T-cells, B-cells, natural killer cells and dendritic cells. It is proposed that cell to cell contact or secretion of soluble factors such as transforming growth factor beta (TGF-ß), hepatocyte growth factor (HGF), indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 and more importantly, interferon gamma (IFN-γ) are responsible (Krampera et al. 2006; Anzalone et al. 2010; Barry and Murphy 2004). Immunosuppression by secretion of soluble factors such as interleukin 6 (IL-6), vascular endothelial growth factor (VEGF) and human leukocyte antigen 6 (HLA) was further confirmed in a study by Weiss et al. (2008) where hUMSCs inhibited the proliferation of concanavalin-A stimulated rat splenocytes and purified T-cells on coculture. In a collagen induced arthritis model, viable hUMSCs were able to reduce disease severity through down regulation of proinflammatory cytokines TNFα, IL-6 and monocyte chemo-attractant protein (MCP-1) while up regulating IL-10 (Lu et al. 2010). Transplantation of 1×10^6 hUMSC cells/kg body weight in patients with systemic lupus erythematosus improved disease outcome in a follow up period of about 2 years. In this study, a balance between Th1 and Th2 related cytokines was restored and patients recorded improved renal function and no relapses were observed (Sun et al. 2010). The immunosuppressant activity of hUMSCs make it a viable option for cell therapy since it reduces chances of rejection and GVHD. This is in contrast to ESCs which may cause an immune reaction on transplantation, as stated earlier. The use of umbilical cord mesenchymal cells has also been studied in cancer treatment. Wang et al. (2012), observed an in vivo and in vitro reduction in tumorigenicity of esophageal carcinoma cells after fusion with hUMSC. Their results revealed the formation of a smaller tumor in SCID mice injected with the hybrid cells compared to mice that received esophageal carcinoma cells. Although hUMSCs possess great potential and properties, they suffer few drawbacks such as reduced differentiation in vivo and low survival after injection. To this end, genetically engineered cells have been proposed, e.g. the activity of IFN-β gene transfected hUMSC was found to be more potent than hUMSC cells on bronchioloalveolar carcinoma cell lines H358 and SW1573 cells (Matsuzuka et al. 2010). Due to increased interest in mesenchymal stem cells as an alternative to ESCs a number of clinical trials are ongoing. Studies indicated reveal the potential use and benefits of hUMSCs as a potential and valuable option in cell based therapies compared to other cells and as such more work needs to be undertaken. Furthermore Wharton's jelly provides a higher frequency of MSC compared to bone marrow at any given isolation procedure (Karahuseyinoglu et al. 2007) and is devoid of the invasiveness involved in BM-MSC harvesting cord blood derived MSC expansion challenges.

Pluripotency has been shown to depend on core regulatory transcription factors such as Oct-4, Nanog and Sox2. Studies that aim to introduce these factors into somatic cells of different origins such as keratinocytes from juvenile adult human hair, dermal papilla cells and human amniotic fluid derived cells (Aasen et al. 2008; Tsai et al. 2010; Li et al. 2009) have exhibited low efficiencies compared to the use of umbilical cord matrix (Cai et al. 2010). Of importance

Table 1 A summary of the advantages and disadvantages of hUMSCs

Advantages	Disadvantages
1. Easily obtained from umbilical cords without invasive procedures involved	Low survival rates after transplantation
2. No risk of viral contamination compared to BMSC	
3. Limited ethical issues involved in comparison to ESCs	
4. Higher rates of harvest compared to cord blood MSCs	Reduced in vivo differentiation potential
5. Can be maintained in culture for longer periods compared to BMSCs	
6. May exhibit clinically low immunogenicity potential	May fail to home at the site of injury after implantation
7. Low tumorigenicity potential as compared to ESCs	
8. Primitive population and express low levels of pluripotent genes such as oct4 and sox2	

Table 2 Clinical trials using hUMSCs for treatment (clinicaltrials.gov)

Study number	Phase/ status	Name of study	Intervention	Design of study
NCT01219465	1and 2; ongoing	Safety and efficacy of umbilical cord mesenchymal stem cells infusion for Initial Type 1 diabetes	Umbilical cord mesenchymal stem cells	Allocation: Non-Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment
NCT01221428	1and 2; ongoing	Safety and efficacy of umbilical cord mesenchymal stem cells infusion for ulcerative colitis	Umbilical cord mesenchymal stem cells i.v infusion	Allocation: Non-Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment
NCT01342250	Completed	Study of human umbilical cord mesenchymal stem cells transplantation for Patients with decompensated liver cirrhosis	Conventional therapy plus low dose hUMSC treatment	Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment

is the fact that hUMSCs have proven to be a primitive population of cells and that they express genes found in ESCs such as Oct4, FGFR4, LIFR. Glut-1, ABCG2, Nanog, Rex-1 and genes of proteins from the three germ layers and trophectoderm were also expressed (Weiss et al. 2006).

From these observations, the umbilical cord matrix seems to be a great source of cells for use in reprogramming since it already expresses the basic genes required for pluripotency, is readily available and not limited by ethics. (Table 1 gives a summary on hUMSCs advantages and disadvantages) On the other hand, since the use of ESCs is limited due to ethical controversies, alternative sources of cells that circumvent this limitation would be highly welcome. To this end, the umbilical cord matrix holds a greater promise.

The possible application of hUMSCs for the treatment of certain human diseases is currently under investigation as shown in Tables 1 and 2 presenting details from recent clinical studies.

Conclusion

As the field of regeneration and transplantation medicine gears towards greater use of cell therapy in

tissue replacements and degenerative diseases, the use of alternative sources of cells other than ESCs is paramount. Of importance will be the use of cells that can be reprogrammed easily and with high efficiencies. Since the umbilical cord seems to be a source of stem cells which already expresses some pluripotent markers, it may prove to be a better alternative compared to other adult stems. To this end more comparative studies involving the reprogramming of hUMSC and other adult stem cells need to be undertaken.

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