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# Umbilical cord blood stem cells – potential therapeutic tool for neural injuries and disorders

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Brain limited self-renewal capability is the main element behind the seriousness of neurodegenerative diseases and neural injuries. Any possible attempts to use cell replacement-therapy approaches rely on; first, the ability of such cells to generate neural cells and tissues with developmental and functional similarities to human brain cells and second, development of safe and effective protocols for cells transplantations. Many recent studies showed that human umbilical cord blood stem cells have the potential to generate cells with neuronal characteristics. It has also been shown that these stem cells have a positive impact on animal models of neural injuries and diseases. Umbilical cord blood stem cells are a potential candidate for clinical therapies for neural injuries and neural degenerative diseases for which current mode of therapy is inadequate. In addition, they might provide an in-vitro model of parenchymal neural cells for toxicology and drugs testing research.

Key words: umbilical cord blood, stem cells, brain, cell therapy

## INTRODUCTION

Stem cells ability to differentiate into different cell types is thought to play a major role in revolutionizing current human medicine. Stem cells unique differentiating features can help in improving current treatment of various diseases and providing functional tissues to repair or even replace diseased tissues. However, using stem cells therapies in regenerative medicine and clinical applications is still under research but showed very promising potential in pre-clinical and some clinical trials (Watt and Contreras 2005, McGuckin et al. 2006, Meier et al. 2006, Harris et al. 2007, Harris 2008). Stem cells are classified, based on their sources, into embryonic stem cells which are derived from the inner cell mass of the blastocyst and adult stem cells such as the stem cells in the bone marrow (Krtolica 2005, Watt and Contreras 2005, Tarnowski and Sieron 2006, Kastenberg and Odorico 2008, Scott and Reijo-Pera 2008). The umbilical cord blood stem cells can be viewed as neither embryonic nor adult stem cells since they are isolated nine months after fertilization and possess differences to both kinds of stem cells, therefore it can be listed as a third source of stem cells (Buzanska et al. 2002, McGuckin et al. 2006, Kucia et al. 2007, McGuckin and Forraz 2008).

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## WHY UMBILICAL CORD BLOOD STEM CELLS?

There has been a great debate on the different stem cells sources for regenerative medicine research and applications. The embryonic stem cells are thought to be the most naive stem cells because they are extracted in the early development stages of the embryo (Thomson et al. 1998, Kogler et al. 2004). Nevertheless, embryonic stem cells have number of limitations. A single embryo produce a limited amount of stem cells even when using feeder layers (Klimanskaya et al. 2005, 2007). Embryonic stem cells lack a fully developed G1 check point, a common characteristic of cancer cells, which increases the chances of acquiring mutations and transformation into tumor cells (Krtolica 2005, Werbowetski-Ogilvie et al. 2009). Recently a boy with ataxia telangiectasia (AT), a rear inherited neurodegenerative disease, developed multifocal brain tumor

after 4 years of treatment by embryonic stem cells injections. Cells from the tumor were non-host stem cells suggesting it was derived from the transplanted cells which was confirmed by microsatellite and HLA analysis (Amariglio et al. 2009). Further to this, embryonic stem cells are often lack the proper imprinting patterns and regulation of certain genes which might lead to spontaneous uncontrolled differentiation and developmental abnormalities (Sapienza 2002, Kogler et al. 2004, Huntriss and Picton 2008). It has also been found that embryonic stem cells increase their immunogenicity by gaining human leukocyte antigens HLA during and after differentiation, which might increase the risk of rejection (Kofidis et al. 2005, Swijnenburg et al. 2005, 2008). Moreover, the isolation of embryonic stem cells from the inner cell mass of the blastocyst involves the destruction of the embryo, which created some serious ethical, religious and political problems. Moving toward effective clinical applications requires a readily and abundant supply of stem cells, first to provide the needed amounts of stem cells and second to provide clinicians with a more accessible and compatible supply of stem cells. Umbilical cord blood can be considered as one of the most abundant sources of non-embryonic stem cells bearing in mind that the global birth rate is over than 200 millions per year (McGuckin et al. 2006, 2008). In addition, unlike the collection of bone marrow, the umbilical cord blood collection is non-invasive and has no side effects on either the baby or the mother (Watt and Contreras 2005, McGuckin et al. 2006, Ballen et al. 2008). Moreover, umbilical cord blood stem cells occupy an intermediate age stage between the embryonic stem cells and the adult stem cells, which lead to a higher proliferating potential and longer telomeres than other somatic stem cells (Pipes et al. 2006, Slatter and Gennery 2006).

Additionally, umbilical cord blood can be stored and cryopreserved in cord blood banks for later uses in transplantations applications. Many cord blood banks have been established in the United Kingdom, France and many other countries worldwide (Watt and Contreras 2005, McGuckin et al. 2006, Lee et al. 2007, Solves et al. 2008).

Furthermore, transplantations of umbilical cord blood showed a lower risk of graft-versus-host diseases (GVHD) than bone marrow transplantations (Rocha et al. 2004, Slatter and Gennery 2006, Mochizuki et al. 2008, Ringden et al. 2008). Rocha and coworkers (2004) have observed that transplanting adult acute leukaemia patients with unrelated umbilical cord blood samples reduced the incidence of grades II, III and IV acute GVHD by 13% in comparison to bone marrow transplantations, while the incidence of chronic GVHD was lowered by 16%. Also, umbilical cord blood transplantation was shown to be associated with lower risk of viral transmission than bone marrow transplantation (Behzad-Behbahani et al. 2005) demonstrating superiority of umbilical cord blood in clinical applications compared to bone marrow. Althought the average sample size of cord blood unit is considered small and limited for single adult transplantation, the immature status of cord blood HLA allowed successful combination of multiple unrelated cord blood units for allogenic transplantations (Ringden et al. 2008)

Another important merit of umbilical cord blood stem cells is their ability to produce induced pluripotent stem cells (iPS) upon transfection with the necessary genes (Giorgetti et al. 2010, Takenaka et al. 2010). Takenaka and coauthors (2010) have successfully reprogrammed CD34$^-$positive cord blood cells into iPS cells after viral transfiction of Oct–4, Sox–2, Klf–4 and C–myc while repressing P53 gene via RNA silencing. The reprogrammed cells resembled normal human embryonic stem cells in many criteria, e.g., cells morphology, differentiation capacity and expression of pluripotent markers. Giorgetti and colleagues (2010) reported similar results after transfecting the cord blood cells with Oct–4 and Sox–2 transcription factors.

Therefore, the umbilical cord blood stem cells can be viewed as the stem cells source of choice for clinical and non-clinical research applications.

## UMBILICAL CORD BLOOD CONTAINS DIFFERENT POPULATIONS OF STEM CELLS

Umbilical cord blood contains a heterogeneous mixture of stem and progenitor cells at different lineage commitment stages (mononuclear fraction of umbilical cord blood cells). The degree of hematopoietic commitment has been studied by tracing some surface antigens including CD133, a marker of multi-lineage stem cells, and CD34, a marker of committed hematopoietic stem cells, using FACS analysis. The potential use of this non-hematopoietic stem cells population in wider range of applications reallocated

efforts to further characterise and investigate the differentiation potential of this unique cells population (McGuckin et al. 2006, Kucia et al. 2007, Kuci et al. 2008, McGuckin and Forraz 2008). Buzanska and others (2002) have successfully purified CD34 and CD45-negative non-hematopoietic stem cells from umbilical cord blood via immunomagnetic cells sorting. Following Buzanska's work, many groups have managed to purify and characterize these primitive population of stem cells from the mononuclear fraction of cord blood using FACS and immunomagnetic depletion strategies (Forraz et al. 2004, McGuckin et al. 2005, 2006, Kucia et al. 2007, McGuckin and Forraz, 2008). McGuckin and coworkers (2005) termed these cells cord blood derived embryonic-like stem cells (CBE's) due to similarities with certain embryonic stem cells characteristics. Another group isolated a characteristically similar population of cells from umbilical cord blood and named them very small embryonic-like stem cells (VSEL) (Kucia et al. 2007). These immature stem cells were found to express pluripotency markers such as Oct–4, Sox–2 and Nanog which are normally expressed by pluripotent embryonic stem cells (Kucia et al. 2007, McGuckin et al. 2008, Orkin et al. 2008). Moreover, they were also positive for stage specific embryonic antigens -3 and -4 (SSEA-3 and SSEA-4), markers of embryonic stem cells (McGuckin et al. 2006, McGuckin and Forraz 2008). These cells have also been successfully differentiated into specialized cells from the three germ layers and therefore can be described as pluripotent stem cells (Ma et al. 2005, Denner et al. 2007, McGuckin et al. 2008).

Umbilical cord blood also contains a population of mesenchymal stem cells that shows different developmental and morphological characteristics to umbilical cord blood pluripotent stem cells (Kang et al. 2006). These mesenchymal stem cells have similar cellular, morphological and differentiation properties to bone-marrow mesenchymal stem cells but, at the same time, show advantages over bone-marrow mesenchymal stem cells that decrease its number and differentiation potential with age (Panepucci et al. 2004, Jeong et al. 2005, Roobrouck et al. 2008).

Cord blood mesenchymal stem cells showed high potential for neural differentiation. Upon sufficient induction, these cells produced cells with neural phenotypes expressing neural markers (El-Badri et al. 2006, Kang et al. 2006, Lim et al. 2008, Kim et al. 2008). Moreover, other groups have shown that these cells can be differentiated into hepatocytes, osteablasts, adipocytes, chondrocytes as well as neural cells (Seo et al. 2009, Bhandari et al. 2010). Oct–4 has been found to be involved in the regulation of cord blood mesenchymal stem cells differentiation emphasizing the stemness characteristics of these cells (Seo et al. 2009).

The abundance, accessibility and differentiation potential of umbilical cord blood stem cell populations made it a promising source of stem cells for research and clinical applications including transplantations (Watt and Contreras 2005, McGuckin and Forraz 2008).

## STEM CELLS IN NEURAL TISSUES

It has been long thought that nervous tissues are incapable of self-repair and renewal, so repair and regeneration of such tissues in the brain after a neurological disorder or injury was considered to be impossible, but the relative recent discovery of the neural stem cells in the brain showed that the brain (part of the central nervous system) has a limited capability of self-repair and structural remodelling following either physiological turnover or a neurological disorder (Johansson et al. 1999, Peterson 2002, Basak and Taylor 2008). The discovery of these neural stem cells made scientists think of using such cells in nervous tissues repair and in treating neurological disorders. But these neural stem cells were reported to be a difficult harvestable population of cells, they can only be collected during necropsy (Palmer et al. 2001, Feldmann and Mattern 2006) and have a very limited number in the central nervous system. These major limitations made the use of these cells for transplantations and clinical applications very difficult, in fact, made it impossible. Therefore finding another source of stem cells with neural potential was very important in order to establish efficient clinical and research protocols.

## NEUROGENIC POTENTIAL OF UMBILICAL CORD BLOOD STEM CELLS

To evaluate the potential role of umbilical cord blood stem cells as a promising therapeutic tool for the treatment of neural diseases, extensive researches focused on the neural capability of these cells. It has been shown that the mononuclear fraction of umbilical

cord blood which contains the pluripotent stem cells along with the mesenchymal stem cells have the potential of becoming neural cells (Lim et al. 2008). It has been shown that umbilical cord blood stem cells have the potential to become mature neuronal cells acquiring mature neuronal phenotypes and expressing mature neuronal specific markers such as neural nuclei (NeuN) and post-synaptic density protein 95 (PSD95) (Domanska-Janik et al. 2006, Habich et al. 2006, Jurga et al. 2006, Korshunova et al. 2007, Ali et al. 2009).

In order to fully understand the neural differentiation potential and pathways of umbilical cord blood stem cells, scientists had to purify and characterize population of interest and study the neural potential of the purified population. McGuckin and coauthors (2008) used negative selection method to purify a pluripotent population of stem cells termed cord blood derived embryonic-like stem cells (CBE's) and showed that these cells have the potential of neural differentiation in-vitro.

As mentioned earlier, pluripotent stem cells are not the only stem cell population in cord blood. Many scientists directed their work toward isolation, purification and characterization of cord blood mesenchymal stem cells. Mesenchymal stem cells from cord blood have been shown to have the capability of neural differentiation (Kang et al. 2006, Wang et al. 2007).

It is clear that different population of stem cells in umbilical cord blood stem cells have the potential of becoming neural cells but in order to move closer towards regenerative medicine clinical applications, these cells must pass the neural functional test first, in another word it is must have electric potential and must be able to generate action potential.

It has been shown that neurons generated from cord blood pluripotent stem cells and mesenchymal stem cells have electrophysiological properties similar to primary neurons (Sanberg et al. 2005, Sun et al. 2005, Jurga et al. 2009). Being able to generate functional neurons from umbilical cord blood stem cells in-vitro is a very important step towards moving into clinical and neural therapeutic applications.

## PRE-CLINICAL TRIALS

The next step towards clinical application is to investigate the safety and therapeutic potential of umbilical cord blood stem cells on animal models of nervous system injuries and neurological diseases.

In humans, many neurodegenerative diseases are associated with ageing, bearing in mind that neurogenesis decreases dramatically with increasing age due to the decline of proliferation of stem/progenitor cells in central nervous system (Bachstetter et al. 2008). Bachstetter and colleagues (2008) found that peripherally injecting aged rat brain with the mononuclear fraction of umbilical cord blood rejuvenated the aged stem/progenitor cells in the brain and stimulated endogenous stem cells to regenerate new cells. This finding suggests a positive impact for umbilical cord blood stem cells in the brain but it does not show if the cells are being incorporated in the brain.

Meier and others (2006) showed that transplantation of mononuclear cells from umbilical cord blood into a damaged brain of a rat model of prenatal brain damage were incorporated in the damaged area of the brain and did facilitate motor neuron recovery. This study demonstrates the therapeutic potential of umbilical cord blood stem cells in brain injuries where the incorporation of cells into the injury site helps the recovery process (Saporta et al. 2003, Meier et al. 2006).

Umbilical cord blood stem cells have also been use on animal models of spinal cord injuries. The stem cells were injected along with brain derived neurotrophic factor (BDNF) into the spinal cord injury site in a rat model. After transplantation, the stem cells differentiated into neural cells at the injury site and showed positive effect on axonal regeneration which induced functional recovery of the rats (Kuh et al. 2005).

Couple of groups transplanted umbilical cord blood stem cells into rats subjected with cerebral artery occlusion in order to induce focal ischemia like pathology. Results showed improvement in animal condition after transplantation and the transplanted cells were detected in the affected cortex, sub-cortex and striatum of damaged brain expressing neuronal markers (Chen et al. 2001, Lu et al. 2002). It is clear that the umbilical cord blood stem cells are capable of incorporation into the damaged locations and neural differentiation *in vivo* which help in the recovery process.

Some other studies used mouse models of certain neurological diseases and investigated the therapeutic potential of umbilical cord blood stem cells on such conditions. In amyotrophic lateral sclerosis (ALS) mouse model, scientists transplanted umbilical cord blood stem cells which resulted in delay of

onset of symptoms and improved the health condition of the animals (Chen and Ende 2000, Ende et al. 2000). However, Habisch and coworkers (2007) could not get the same positive results on his transgenic ALS mice model and suggested that the cell dosage and transplantation strategies need to be optimised in order to achieve the positive therapeutic impact.

It is clear that umbilical cord blood stem cells have a potential therapeutic impact on animal models of acute nervous injuries (brain and spinal cord) as well as certain types of slowly-progressive neurodegenerative diseases.

## CLINICAL TRIALS

Umbilical cord blood clinical practices started in 1972 to treat lymphoblastic leukaemia (Ende and Ende 1972). Later it was used as a regular transplant, as a replacement for bone marrow transplantations, to treat haematological malignancy or bone marrow failure after any chemotherapy side effects (Gluckman et al. 1989). Initially, umbilical cord blood clinical applications were restricted to blood diseases therapies (Gluckman et al. 1989, Slatter et al. 2006). However, the ability of producing different types of cells (from the three germs layers) from umbilical cord blood stem cells has highlighted its therapeutic potential in treating wide range of pathological disorders including neurological diseases and injuries (Watt and Contreras 2005, McGuckin et al. 2006, Denner et al. 2007, McGuckin and Forraz 2008).

The use of umbilical cord blood stem cells in neural clinical applications is still at its early stages but results obtained so far are very promising. Kang and coworkers (2005) purified mesenchymal stem cells from umbilical cord blood and used them to treat a 37 years old woman with a spinal cord injury. The cells were transplanted at the injured location and results showed regeneration of injured spinal cord at the injured site and patient showed improved sensory perception and mobility (Kang et al. 2005). In another clinical trial sponsored by Duke university started in January 2008, scientists are studying the potential of umbilical cord blood autologous transplantation as a treatment tool for babies born with brain damage (neonatal hypoxic ischemic encephalopathy). The duration of study is 2 years and is estimated to be completed in 2010.

## CONCLUSION

Umbilical cord blood can be viewed as the most promising source of stem cells for research and clinical applications. It is abundant supply, immunological immaturity and high plasticity made it superior to other sources of stem cells. Umbilical cord blood stem cells showed high potential for neural differentiation and scientists were able to produce functional neural cells from these stem cells. Pre-clinical trials on animal models showed promising results toward moving into clinical trials and treatment of neural diseases and injuries. Clinical trials are still at its early stages but results obtained so far demonstrated high potential and hope toward developing effective therapies for neural disorders and injuries.

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