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REVIEW

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Umbilical cord: an unlimited source of cells differentiable towards dopaminergic neurons

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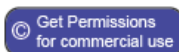
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Abstract

Cell replacement therapy utilizing mesenchymal stem cells as its main resource holds great promise for ultimate treatment of human neurological disorders. Parkinson's disease (PD) is a common, chronic neurodegenerative disorder hallmarked by localized degeneration of a specific set of dopaminergic neurons within a midbrain sub-region. The specific cell type and confined location of degenerating neurons make cell replacement therapy ideal for PD treatment since it mainly requires replenishment of lost dopaminergic neurons with fresh and functional ones. Endogenous as well as exogenous cell sources have been identified as candidate targets for cell replacement therapy in PD. In this review, umbilical cord mesenchymal stem cells (UCMSCs) are discussed as they provide an inexpensive unlimited reservoir differentiable towards functional dopaminergic neurons that potentially lead to long-lasting behavioral recovery in PD patients. We also present miRNAs-mediated neuronal differentiation of UCMSCs. The UCMSCs bear a number of outstanding characteristics including their non-tumorigenic, low-immunogenic properties that make them ideal for cell replacement therapy purposes. Nevertheless, more investigations as well as controlled clinical trials are required to thoroughly confirm the efficacy of UCMSCs for therapeutic medical-grade applications in PD.

Keywords: *nerve regeneration; umbilical cord; mesenchymal stem cells; differentiation; neuronal; dopaminergic neurons; dopamine; substantia nigra; ventral mesencephalon; Parkinson's disease; cell replacement therapy; neural regeneration*

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Introduction

Cell replacement approaches for ultimate treatment of degenerative disorders by replenishing lost cells with fresh and functional ones largely rely on differentiation of potential cell sources. This is mainly because cell loss plays a central role in onset and progression of degenerative diseases (Fox et al., 2014).

Parkinson's disease (PD) is a typical neurodegenerative disorder characterized by progressive but largely localized degeneration of dopaminergic (DAergic) neurons chiefly within midbrain substantianigra pars compacta (SNpc) (Hirsch et al., 1997). Current pharmacotherapeutic approaches include administration of dopamine precursors such as L-dihydroxy phenyl alanine, dopamine agonists, monoamine oxidase B inhibitors, catechol-O-methyltransferase inhibitors and adenosine A2A antagonists (Stocchi, 2014), blockage of dopamine D3 receptors (Cortés et al., 2016), inhibition of neuronal nitric oxide synthase (Maccallini and Amoroso, 2016) and use of small-molecule epigenetic modifiers (Hegarty et al., 2016). Moreover, other alternatives such as surgical options, mainly deep brain stimulation, are being used in patients with advanced PD (Odekerken et al., 2013). Nevertheless, these treatments solely provide symptomatic relief and are not able to hinder disease progression. In this review, the potential therapeutic application of umbilical cord mesenchymal stem cells (UCMSCs) in PD will be discussed with an exclusive focus on generation of DAergic neurons.

In Search of Cell Sources for PD Cell Replacement: Criteria

The proof-of-principle for feasibility of cell replacement therapy (CRT) in PD is provided by the fact that clinical transplantation of human fetal tissues (in the open-label trials) obtained from ventral mesencephalon results in striatal re-innervation of DAergic neurons and symptomatic relief (Lindvall and Björklund, 2004). Cell replacement therapy (CRT) is aimed at constitution of a neuroprotective and/or neuroregenerative platform for human neurological disorders such as PD. However, prior to clinical translation of stem cells for PD, a number of requirements need to be taken into account in order to opt for a suitable cell type. They include 1) a standardized, medical grade differentiation protocol with minimum reliance on various growth factors, chemicals and any animal components; 2) phenotypical resemblance of cell sources upon differentiation. In the case of PD, stem cell-derived DAergic neurons have to display DAergic phenotype, express DAergic markers such as Pitx3, Nurr1, Engrailed-1, Lmx1a, tyrosine hydroxylase, aromatic acid decarboxylase and vesicular monoamine transporter and release dopamine in a controlled fashion. They must also display electrophysiological characteristics of substantia nigra (SN) neurons; 3) long-term survival of grafted DAergic neurons in the target tissue; 4) active integration into local neural network; target DAergic neurons should augment effective reconstitution of neural circuits and integrate into host striatum; 5) functionality of engrafted cells; functional DAergic

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neurons have to alleviate Parkinson's symptoms and improve behavioral motor conditions after transplantation in a rodent PD model without causing any sign of tumorigenicity and dyskinesias (Brundin and Hagell, 2001; Isacson et al., 2003; Braak and Del Tredici, 2008). It is noteworthy that transplantation of differentiated cells into various sub-regions in the striatum where A8, A9 and A10 dopaminergic cell groups extend their fibers to release dopamine would increase the chance of recovery and movement restoration in animal models of PD. On the other hand, impurities carrying non-DAergic neurons in our cell reservoir could offer therapeutic advantages to pure sources for cell therapy because not just dopaminergic but also neuronal types of serotonergic and others are damaged in the course of PD.

In Search of Cell sources for PD Cell Replacement: Candidates ↑

Cell sources are categorized based on their potentiality to undergo DAergic differentiation into endogenous and exogenous candidates. Endogenous candidates include primary cultures of ventral mesencephalon (VM) that consist of DAergic progenitor cells and neural stem cells from subventricular zone, striatum (ST) and SN (Fallon et al., 2000; Storch et al., 2004; Mohapel et al., 2005; Madhavan et al., 2009). Exogenous sources, on the other hand, include embryonic cells, induced pluripotent stem cells (iPSCs) and also mesenchymal stem cells derived from bone marrow, amniotic fluid, Sertoli cells [More Details](#), retinal pigment epithelium (RPE), adipocytes, carotid body cells, adrenal medullary, cervical sympathetic ganglion neurons and olfactory mucosal cells (Bankiewicz et al., 1988; Espejo et al., 1998; Subramanian et al., 2002; Nakao et al., 2004; McLaughlin et al., 2006; Levy et al., 2008; Murrell et al., 2008; Glavaski-Joksimovic et al., 2009). These cell candidates have already been subjected to various treatments with inducing factors by adding these factors to cell medium and also by gene transfer to direct them towards DAergic fate. In addition, co-culture systems have been established by several helper cell lines including fibroblasts, pA6 stromal cell line, sertoli cells, RPE, as reviewed by Gardaneh (2010). They appear to secrete medium specific growth factors capable of inducing DAergic phenotype when interacting with the target cells. Furthermore, we previously proposed a combined, multi-factorial approach based on interaction of GPX-1-overexpressing DAergic neurons, GDNF secreting astrocytes and Nurr1-expressing microglia to potentiate survival and biological function of DAergic neurons against 6-OHDA toxicity (Gardaneh et al., 2010).

Mesenchymal Stem Cells (MSCs) versus Embryonic Stem Cells (ESCs) ↑

Stem cells are regarded as undifferentiated cells that can undergo both proliferation and differentiation (Fuchs and Segre, 2000). ESCs are stem cells derived from the inner cell mass of the blastocysts (Thomson, 1998). MSCs are non-hematopoietic adult stem cells that possess the capacity to differentiate into various tissues including bone, cartilage and adipose tissue (Pountos and Giannoudis, 2005). MSCs can be isolated from bone marrow (Bianco et al., 2001), adipose tissue (Zuk et al., 2001), cord blood, amniotic fluid (In't Anker, 2003) and placental tissue (Karahuseyinoglu et al., 2007).

MSCs have been described as plastic adherent multipotent cells represented by distinct terminologies such as “colony-forming fibroblastic cells” (Kuznetsov et al., 1997), “bone marrow stromal cells (BMSC)” (Peister, 2004), “multipotent adult progenitor cells” (Jiang et al., 2002) and “marrow isolated adult multi-lineage inducible cells” (D'Ippolito, 2004; Boroujeni et al., 2012). ESCs may appear as an appealing source for any cell-based therapy but their possible complications such as tumor formation, the need for immunosuppression, limited ESCs supply and above all, ethical concerns have substantially restricted their therapeutic use. Therefore, the employment of MSCs in the tissue regeneration has attracted great interest as therapeutic agents. Moreover, these cells are capable of treating a variety of maladies including spinal cord injury (Hofstetter et al., 2002) and stroke (Chen et al., 2001), although UCMSC-derived dopaminergic neurons have not been utilized in the clinic. This means that steps have to be taken to clarify both beneficial and deleterious consequences of such a therapy for human patients.

The plasticity and transdifferentiation capacity of MSCs have provided an effective platform as they differentiate into other lineages of ectodermal and endodermal cells. Mezey et al. (2000) initially described the *in vivo* differentiation of transplanted adult bone marrow cells into glial cells. To be utilized specifically for PD cell therapy, studies have reported the feasibility of neuronal differentiation of MSCs in which the paracrine effect of the cells has been taken into account (Kitada and Dezawa, 2012).

Umbilical Cord: a Reservoir of MSCs ↑

The umbilical cord consists of two umbilical arteries and also one umbilical vein which delivers oxygenated, nutrient-rich blood to the fetus (Meyer et al., 1978). This vascular structure is buried within a jelly-like tissue called umbilical cord matrix or Wharton's jelly which is counted as the gelatinous connective tissue (Wang et al., 2004). These cells express MSC markers SH2 and SH3 but not CD35 and CD45 which are regarded as hematopoietic markers. In addition, they exhibit the capacity to differentiate into a wide range of lineages including adipocytes, osteocytes, chondrocytes, and neural lineages (Mitchell et al., 2003; Wei et al., 2012). UCMSCs have shown scores of advantages over other stem cell sources outlined below: 1) they exist in more primordial stages of differentiation than other mesenchymal cells including BMSCs (Hao et al., 1995). 2) They do not express many of immunological markers involved in tissue rejection as shown by successful transplantation of umbilical cord blood nucleated cells in a 23-month-old child suffering from hemophagocytic lymphohistiocytosis (Schwinger et al., 1998). 3) Isolation, expansion, and freezing of these cells are easier and less expensive compared to many other sources such as neural stem cells (Taghizadeh et al., 2011; Dalous et al., 2012). 4) They demonstrate high proliferation rate compared to BMSCs (Baksh et al., 2007; Boroujeni et al., 2012). 5) They can be genetically manipulated to express various factors and/or used as delivery vehicles for therapeutic

applications (Kim et al., 2008; Li et al., 2013; Zhang et al., 2014).

Dopaminergic Differentiation of UCMSCs



Production of functional DAergic neurons relies fundamentally on signaling factors such as Shh, FGF8 and Wnt1 that initiate DAergic neurogenesis. Subsequently, the gene expression of LIM homeodomain family members (Lmx1a, Lmx1b) and FoxA2 facilitates specification of DAergic progenitors, which paves the way for terminal differentiation, promoted by cooperative function of Nurr1 and Pitx3 (Chakrabarty et al., 2012; Hegarty et al., 2013). In order to demystify the precise mechanisms of DAergic differentiation in MSCs, early events parallel with late events need to be examined. Such studies will clarify the innate preparedness and potential of MSCs for neuronal/DAergic differentiation.

Reports indicate that UCMSCs are capable of displaying neuronal phenotype by expressing neuron-specific enolase (Mitchell et al., 2003), astrocytic marker GFAP and oligodendrocytic marker CNPase (Ha et al., 2004; Tracy et al., 2008). The UCMSCs can be induced to differentiate into DAergic neurons comparatively to a high or low degree of success as shown in [Table 1]. These studies mainly applied transcription factors and/or growth factors as transgenes from within or as supplements from outside cells as inducing forces for neurogenesis and neuroprotection. Inclusion of exogenous genes in target cells that are destined to be part of patients' live tissue can be a source of biological and ethical concerns. It is not possible to readily predict the physiological consequences of exogenous gene expression, neither are scientists prepared to fully satisfy the society of unforeseeable complications inherent with transgene transfer into human body. Further, undifferentiated UCMSCs were used for transplantation and mostly resulted in behavioral recovery in animal models of PD based on parkinsonian toxins 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) or rotenone. For instance, Weiss et al. (2006) and Xiong et al. (2010) merely used undifferentiated UCMSCs without applying any growth factors for transplantation and made promising observations for decreased rotations by 50% and 67% respectively. Other investigators employed several inducing factors including epidermal growth factor (EGF), sonic hedgehog (SHH), nerve growth factor (NGF) and/or specific conditioned media (e.g., from amniotic epithelial cells, AEC) to facilitate DAergic neuron production and, upon PD brain transplantation, observed alleviation of motor symptoms (Fu et al., 2006; Li et al., 2010; Kang et al., 2013; Shetty et al., 2013; Yang et al., 2013a; Zhao et al., 2016). Our laboratory has recently tested the inducing effect of murine cerebrospinal fluid on DAergic differentiation of UCMSCs which were then transplanted to rat striatum (Aliaghaei et al., 2016). The cells survived and resulted in rotational recovery and reduced rate of neuronal apoptosis in animal's injured brain. Besides, we successfully generated MSCs-derived DAergic secreting neurons using a cocktail of choroid plexus epithelial cells-conditioned medium and knockout serum replacement (Boroujeni et al., 2017). A combinatorial approach to convert UCMSCs to DAergic neurons employed both transgenes (such as Lmx1a and neurturin, NTN) and external inducing factors (basic fibroblast growth factor, β -mercaptoethanol, SHH, fibroblast growth factor-8, retinoic acid) that upon cell transplantation demonstrated improvements in behavioral deficits against MPTP (Yan et al., 2013). Measures outlined above could pave the ground for survival as well as regeneration of host neurons and ultimately for augmented efficacy of repairing target neural tissues. In accordance with this notion, MSCs transplanted into the brain stimulate endogenous neuronal growth and synaptogenesis and enhance functional recovery of damaged neurons (Lin et al., 2011; Olson et al., 2012). These trophic effects are implemented by MSC-mediated secretion of a variety of cytokines and neurotrophic factors (Joyce et al., 2010). Besides, the analysis of UCMSCs conditioned medium secretome revealed it contains neuro-regulatory components [such as Cyr61 protein and colony-stimulating factor 1 (CSF-1)] essential for the maintenance and maturation of neural stem cells, respectively (Pires et al., 2016). Hence, it is important in these studies to distinguish between neurogenic and paracrine protective effects of the administered UCMSCs so their fate as well as their ultimate therapeutic effects can be clearly determined.

Year	Author(s)	Transgene	Inducing Factor
2003	Mitchell et al.	None	None
2004	Ha et al.	None	None
2006	Weiss et al.	None	None
2010	Xiong et al.	None	None
2011	Lin et al.	None	None
2012	Olson et al.	None	None
2013	Yan et al.	Lmx1a, NTN	EGF, SHH, NGF, B27
2013a	Yang et al.	None	EGF, SHH, NGF, B27
2013b	Shetty et al.	None	EGF, SHH, NGF, B27
2016	Zhao et al.	None	EGF, SHH, NGF, B27
2017	Boroujeni et al.	None	Choroid plexus epithelial cells-conditioned medium, knockout serum replacement

Table 1: Umbilical cord mesenchymal stem cells-based therapy for *in vitro* generation of dopaminergic neurons

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MiRNAs-Mediated Neuronal Differentiation of UCMSCs



In order to develop UCMSCs-based therapeutic strategies, a comprehensive understanding of signaling pathways involved in proliferation and differentiation of UCMSCs is needed. These biological processes are considerably modulated by genetic and epigenetic mechanisms. Recently, microRNAs (miRNAs) as small non-coding RNA have been demonstrated to play essential roles in a plethora of biological functions including neural differentiation and neurodegeneration (Christensen and Schratt, 2009). Extensive studies have been carried out and shed light on the gene expression profile of miRNAs involved particularly in neurogenesis. For instance, miR-124a and miR-9 have been regarded as most specific and well-studied brain miRNAs which promote neural differentiation (Liu and Zhao, 2009). Four miRNAs (miR-1290, miR-26b, miR-194, and miR-124a) have been recently shown to be up-regulated during neuronal differentiation of UCMSCs. This study also disclosed two down-regulated miRNAs (miR-4521 and miR-543) with unknown functions in neurogenesis (Zhuang et al., 2015). Moreover, Meng et al. (2016) compared the gene expression profile of miRNAs in umbilical cord and cord blood-derived MSCs and interestingly demonstrated that the expression of genes related to neurogenesis was increased in UCMSCs, which is contrary to the finding performed by Secco et al. (2009). This dissimilarity demands a detailed investigation into miRNA signature of tissue-specific MSCs prior to any clinical application.

As mentioned above, miRNAs have critical roles in cellular processes. Autophagy is a self-degradation process of

cytosolic components, in which defective cellular constituents are degraded through delivery to lysosomes. A recent study has suggested the significant implication of autophagic flux in neural differentiation (Vessoni et al., 2011). Indeed, genetic ablation of Atg5 and Atg7, both involved in autophagic machinery, in the mouse brain has been shown to lead to neurodegenerative disorders (Nikoletopoulou et al., 2015). Further, emerging evidence indicates a strong link between miRNA regulatory networks and autophagy pathways (Frankel and Lund, 2012). Thus, miRNA-autophagy interactions during neuronal differentiation of UCMSCs should be well elucidated to improve the therapeutic potential of UCMSCs.

Conclusion

Pharmacotherapeutic options (including Mitoquinone, PYM50028 and Rasagiline) hitherto failed to improve PD patients in recent clinical trials, despite their great promise in experimental researches (Athauda and Foltynie, 2015). Likewise, Levodopa administration to restore dopamine levels causes dyskinesia few years after treatment initiates (Prashanth et al., 2011). Moreover, the new drug development process is very costly and time-consuming (Sherer et al., 2012). MSCs-based approaches have opened a promising avenue into treatment of patients with neurological disorders such as PD. In this review, the potential therapeutic application of UCMSCs in PD patients was outlined. As discussed above, due mainly to their non-tumorigenic as well as low immunogenic capacity, UCMSCs could be considered as suitable cell candidates for neuro-regeneration and neuro-repair in treating neurodegenerative diseases with specific focus on PD. Above and beyond, the release of dopamine by UCMSCs has to be under control by measures such as use of regulating genetic elements. However, clinical trials using UCMSCs for PD have not been registered in ClinicalTrials.gov (in April 2017) whereas for other brain diseases, studies are in progress as shown in [Table 2]. The completed studies are basically indicating that UCMSCs are stable and safe. Considering collected data from clinical trial failures related to neuroprotective drugs, enriched comprehension of mechanisms underlying PD is highly demanded if CRT is being employed. Additionally, the detailed outcomes of these trials will surely assist in setting up improved methods of cell preparation, purification and DAergic neuron enrichment, pre-injection cell manipulation, transplantation procedures, cell integration to neural network and their paracrine effects beside long-term potential recovery from PD symptoms.

Study ID	Study Title	Phase	Status
NCT01451111	Phase I/II Study of the Safety and Efficacy of Intracerebral Transplantation of Human Umbilical Cord Mesenchymal Stem Cells in Parkinson's Disease	I/II	Completed
NCT01451112	Phase I/II Study of the Safety and Efficacy of Intracerebral Transplantation of Human Umbilical Cord Mesenchymal Stem Cells in Parkinson's Disease	I/II	Completed
NCT01451113	Phase I/II Study of the Safety and Efficacy of Intracerebral Transplantation of Human Umbilical Cord Mesenchymal Stem Cells in Parkinson's Disease	I/II	Completed
NCT01451114	Phase I/II Study of the Safety and Efficacy of Intracerebral Transplantation of Human Umbilical Cord Mesenchymal Stem Cells in Parkinson's Disease	I/II	Completed
NCT01451115	Phase I/II Study of the Safety and Efficacy of Intracerebral Transplantation of Human Umbilical Cord Mesenchymal Stem Cells in Parkinson's Disease	I/II	Completed
NCT01451116	Phase I/II Study of the Safety and Efficacy of Intracerebral Transplantation of Human Umbilical Cord Mesenchymal Stem Cells in Parkinson's Disease	I/II	Completed
NCT01451117	Phase I/II Study of the Safety and Efficacy of Intracerebral Transplantation of Human Umbilical Cord Mesenchymal Stem Cells in Parkinson's Disease	I/II	Completed
NCT01451118	Phase I/II Study of the Safety and Efficacy of Intracerebral Transplantation of Human Umbilical Cord Mesenchymal Stem Cells in Parkinson's Disease	I/II	Completed
NCT01451119	Phase I/II Study of the Safety and Efficacy of Intracerebral Transplantation of Human Umbilical Cord Mesenchymal Stem Cells in Parkinson's Disease	I/II	Completed
NCT01451120	Phase I/II Study of the Safety and Efficacy of Intracerebral Transplantation of Human Umbilical Cord Mesenchymal Stem Cells in Parkinson's Disease	I/II	Completed

Table 2: Current trials using human umbilical cord mesenchymal stem cells (UCMSCs) for neurological disorders (retrieved from ClinicalTrials.gov, April 2017)

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