Neuroscience and Biobehavioral Reviews xxx (2011) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Recent progress in cell therapy for basal ganglia disorders with emphasis on menstrual blood transplantation in stroke

Maria Carolina Oliveira Rodrigues[a,b,**], Julio Voltarelli[b], Paul R. Sanberg[a], Julie G. Allickson[c], Svitlana Garbuzova-Davis[a], Cesar V. Borlongan[a,*]

[a] Department of Neurosurgery and Brain Repair, University of South Florida College of Medicine, 12901 Bruce B. Downs Blvd., Tampa, FL, USA
[b] Department of Internal Medicine, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil
[c] Cryo-Cell International, Inc., Tampa, FL, USA

ARTICLE INFO

Article history:
Received 21 January 2011
Received in revised form 25 April 2011
Accepted 20 May 2011

Keywords:
Cell-based therapy
Menstrual blood stem cells
Endometrium-derived stem cells
Basal ganglia disorders
Stroke
Parkinson's disease
Huntington's disease

ABSTRACT

Cerebrovascular diseases are the third leading cause of death and the primary cause of long-term disability in the United States. The only approved therapy for stroke is tPA, strongly limited by the short therapeutic window and hemorrhagic complications, therefore excluding most patients from its benefits. Parkinson's and Huntington's disease are the other two most studied basal ganglia diseases and, as stroke, have very limited treatment options. Inflammation is a key feature in central nervous system disorders and it plays a dual role, either improving injury in early phases or impairing neural survival at later stages. Stem cells can be opportunely used to modulate inflammation, abrogate cell death and, therefore, preserve neural function. We here discuss the role of stem cells as restorative treatments for basal ganglia disorders, including Parkinson's disease, Huntington's disease and stroke, with special emphasis to the recently investigated menstrual blood stem cells. We highlight the availability, proliferative capacity, pluripotentiality and angiogenic features of these cells and explore their present and future experimental and clinical applications.

Contents

1. Current status of stroke

Cerebrovascular diseases are the third leading cause of death (Xu et al., 2010a) and the primary cause of long-term disability in the United States (Centers for Disease Control and Prevention, 1999). Although the incidence and mortality have decreased over the years, stroke remains a major concern in the clinical setting

* Corresponding author. Tel.: +1 813 974 3154; fax: +1 813 974 3078.
** Corresponding author at: University of South Florida, College of Medicine, Department of Neurosurgery and Brain Repair, 12901 Bruce B. Downs Blvd, Tampa, FL, United States. Tel.: +1 813 974 3154; fax: +1 813 974 3078.
E-mail address: cborlong@health.usf.edu (C.V. Borlongan).

0149-7634/$ – see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.neubiorev.2011.05.010

largely due to the limited treatment currently available. 15–30% of first time stroke patients become permanently disabled and that 20% still require institutional care 3 months after stroke (Asplund et al., 1998). Moreover, the American Heart Association reports estimated direct and indirect costs of stroke of $73.7 billion for the year of 2010 (Lloyd-Jones et al., 2010), indicating that this disease negatively impacts on the economic productivity of our society. Therefore, every effort to decrease the incidence of strokes and to, at least, minimize their devastating sequelae is urgently warranted.

To date, the best available therapeutic agent is tissue plasminogen activator (tPA), which is indicated for ischemic stroke. The drug catalyzes the transformation of plasminogen into plasmin, which acts as a potent thrombolytic agent and is used to restore the blood flow, thus minimizing immediate tissue death. In 1995, an American clinical trial demonstrated that patients treated with tPA within 3 h of beginning of symptoms presented less disability 3 months later (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995) and the results were also supported by a similar concomitant European trial (Hacke et al., 1995). Since then, the American Food and Drug Department (FDA) and, later, the European Medicines Agency have approved the drug and it has been applied as standard therapy in emergency rooms all over the world. Numerous other studies also supported the early use of tPA, demonstrating a direct correlation between time elapsed to begin treatment and long-term neurological impairment (Alexandrov et al., 2001; Marler et al., 2000; Rha and Saver, 2007).

The therapeutic window of 3 h, however, is a major barrier to tPA clinical application, since most of patients are not able to reach an Emergency Room and complete the Neurologic triage within that timeframe. It was estimated in 2008 that only 1.8–2.1% of all patients affected by ischemic strokes in the United States had received the therapy (Kleindorfer et al., 2008). Further studies have tried to evaluate the possibility of extending the limit beyond 3 h, but there were mixed results, with an increase in mortality due to hemorrhagic complications (Carpenter et al., 2011; Cronin, 2010; Hacke et al., 2008). The exciting initial outcome of tPA therapy necessitated more careful analyses. Indeed, subsequent studies showed that the results of tPA treatment were not as favorable as once suggested and, most importantly, that its beneficial effects were restricted to a small population of the stroke patients. In 2006, the European data were analyzed, and indicated that male gender, history of previous strokes, higher age, co-morbidities, such as hypertension and diabetes, and higher severity of the stroke were associated with poor outcomes after tPA therapy (Kent et al., 2006). Moreover, new research has shown that while tPA renders clot clearance within the intravascular space, it can be deleterious to the brain through worsening of the already altered blood–brain barrier permeability, in addition to the direct neurotoxic effects reported by Yepes et al. (2009). In summary, treatment of stroke is still very limited. It is clear that tPA for ischemic stroke benefits a very select group of patients, while those unfortunate patients not able to avail of the 3-h tPA efficacy period will have to deal with the long-term consequences of the disease. For these, restorative interventions may offer some benefits to sub-acute and chronic ischemic stroke patients.

2. The role of inflammation in stroke and other neurodegenerative conditions

The acute blood supply interruption that takes place in ischemic stroke promotes almost instant cell death of the infarct core. The surrounding tissue comprises the penumbra area, which retains structural integrity, but lacks function. It has a less defined outcome, and may either evolve to death or to recovery, depending on the severity of the ischemia and on the reestablishment of blood flow within the first hours after stroke (Green et al., 2003). In the penumbra area, once the hypoxic insult is settled, a complex cascade of inflammatory events is initiated by microglial activation, resulting in blood–brain barrier leakage, edema, hemorrhage and leukocyte infiltration (Amor et al., 2010; Emsley et al., 2008).

Microglial activation is also described in Parkinson's, Alzheimer's and Huntington's disease (Brochard et al., 2009), both in experimental models and human post-mortem tissue. Ouchi et al. (2009) demonstrated, through positron emission tomography (PET), progressive activation of microglia and concomitant decrease of dopaminergic neurons in brains of live Parkinson's disease patients. Likely, Tai et al. (2007) showed microglial activation in live presymptomatic Huntington's disease gene carriers.

Attracted by the microglia, neutrophils and monocytes are the first leukocytes to migrate into the CNS, followed by dendritic cells and lymphocytes, among which cells with regulatory functions (Gelberblom et al., 2009). Neutrophils are considered the main mediators of brain injury after reperfusion, and experimental studies correlate their accumulation with the severity of brain tissue damage and poor neurological outcome (Atochin et al., 2000; Matsuo et al., 1994). Once in the cerebral parenchyma, these cells contribute to the amplification of the inflammatory reaction, releasing cytokines, activating resident cells, attracting more cells from the peripheral circulation and activating proteases, all of which lead to further cell death (Jin et al., 2010).

In the last 15 years, research has targeted inflammatory components of stroke, aiming to reduce the extension of injury in the central nervous system (CNS). Anti-inflammatory interventions may attenuate the secondary cell death associated with ischemic stroke and, likely, lessen neurological impairments among other progressive disabilities. Experimental studies have shown that suppression of the inflammatory response after stroke leads to reduction of the infarct size (Connolly et al., 1996; Hurn et al., 2007). However, the side effects of the systemic immunosuppression promoted by these approaches, such as infections, limit their clinical application. Specific inflammatory agents have been targeted in experimental models, with variable results (Banwell et al., 2009; Fan et al., 2009; Wang et al., 2004; Yilmaz and Granger, 2010). Although the ICAM-1 antagonist showed exciting outcomes in the experimental setting, they were not reproduced by the clinical trial (Enlimomab Acute Stroke Trial Investigators, 2001). Others have focused on more general interventions, also trying to abrogate inflammation, such as induced hypothermia, corticosteroids and minocycline (Faraji et al., 2009; Linares and Mayer, 2009; Matsukawa et al., 2009), some of which are currently being evaluated in clinical trials.

Inflammation plays a double edged sword in stroke and in neurodegenerative conditions. While it can be deleterious to the integrity of the CNS, it is also necessary for repair. Some of the inflammatory agents, such as IL-6, nitric oxide (NO) and TNF-α, have antagonistic effects on the tissue, acting as protective in early phases and detrimental in late stages of injury (Luheshi et al., 2009; McCoy and Tansey, 2008; Suzuki et al., 2009). The microglia stimulate the infiltration of immune cells, release toxic molecules such as free radicals, arachidonic acid, pro-inflammatory cytokines and therefore contribute to cell death. On the other hand, they phagocyte debris and produce neurotrophic factors, important for tissue repair. Astrocytes have supportive functions in the CNS, including scavenge of neurotransmitters released during synaptic activity, water and ion homeostasis, production of neurotrophic factors, integrity of the blood–brain barrier and control of the microvascular tonus in the CNS (Takano et al., 2009). Failure of any of the supportive functions jeopardizes neuronal survival. Additionally, reactive astrocytes contribute to the formation of glial scar, therefore limiting the extension of injury. In long-term, however,

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the scar mechanically restrains the blood supply and migration of cells and, therefore, hampers repair of the injured tissue. Interestingly, Faulkner et al. (2004) demonstrated that the inhibition of astrocyte activation following spinal cord injury increased neuron death, possibly because even in an injured environment, astrocytes still maintain some supportive functions, including the secretion of neurotrophic factors (NGF and BDGF), which are important for tissue repair and modulation of synaptic plasticity (Kriz, 2006).

In summary, inflammation may afford benefits to the brain during the early stages of neural cell death. However, during the chronic period, if inflammation persists and no therapeutic intervention is employed to correct this aberrant response, then such host tissue response to injury will exacerbate the disease progression. In several aspects, the inflammatory mechanisms described after stroke resemble those also observed in chronic, neurodegenerative diseases, in which inflammation is also a key feature. In fact, most of the knowledge about the pathogenesis of stroke derives from previous studies in Parkinson's, Huntington's and Alzheimer's diseases (Park et al., 2009a). After an initial trigger, microglia activation takes place, initiating a chronic inflammatory reaction, which frequently leads to tissue destruction (Wyss-Coray and Mucke, 2002). Along this line, the initiation of anti-inflammatory regimens for stroke and neurodegenerative diseases is critical to the resulting outcome and it represents an opportune niche for the application of cell-based therapies. Additional critical analyses of inflammation as a friend and foe of stroke are needed to fully decipher the mechanisms of action of inflammation in disease onset and progression.

3. Critical therapeutic window for cell therapy in stroke

Injury following stroke can be divided in three consecutive stages, important for the different therapeutic opportunities implied in each (Hess and Borlongan, 2008). In the 24 h that immediately follow stroke, attempts to restore the blood flow would be neuroprotective, therefore preventing further early neuronal death and restricting the extent of the penumbra area. Thereafter, once the injury is established, the interventions would be mainly restorative and cell-based therapies would have their best indications. It is known from animal studies that during the first month after stroke the brain produces inflammatory signals, which can be used to opportunely attract cells injected in the systemic circulation to the site of injury (Hill et al., 2004). Although most intravenously injected cells are trapped in peripheral organs and readily eliminated, studies describe neurological restoration despite the low number of cells that effectively reach the inflammatory target (Detante et al., 2009; Park et al., 2009a). It is also during this inflammatory period that the interventions may restore the viability of the tissue in the penumbra area. Terminated the first month, inflammation decreases and scars and structural damage persist. Stem cells still have a possible therapeutic role in this last phase, but they should be delivered directly into the nervous tissue, through the aid of scaffolds and surgical procedures.

Stem cells opportunely interact with the inflammatory dynamics of stroke, modulating its harmful effects and maximizing its regenerative potential. To this end, finding a novel approach directed at the sub-acute injury phase of stroke, such as the use of cell therapy against secondary inflammatory response, to at least minimize the injuries and at most reverse the outcome of stroke is a logical therapeutic approach towards improving the quality of life for many stroke patients. One of the major difficulties in stem cell therapy is to find an adequate source of cells, readily available for applications, without time-consuming manipulations. Ideally, autologous sources would be preferred, avoiding rejection and allowing longer permanence of engrafted cells in the targeted tissue. Concerning stroke, the short time window after the event frequently limits the use of autologous cells, which in most cases need to be collected and expanded before delivery. Fortunately, mesenchymal or stromal cells are suitable candidates for allogeneic application, due to their low immunogenicity (Yagi et al., 2010). Although ultimately rejected by the host immune system, these cells remain long enough within the tissue to promote tissue repair, without immunosuppression (Westrich et al., 2010).

4. Mechanisms of therapeutic targets for stem cells

Although the knowledge about cell-based therapy for stroke and other neurological diseases has increased over the years, there is no consensus about how the cells should be administered and even about which types of cells are most effective (Banerjee et al., 2011). In the past years, several studies have addressed the issue, with relevant contributions to the field. First, transplanted cells have limited survival in the host, whether injected locally or systemically (Jablonska et al., 2010; Mitrecić et al., 2010). This observation, although at first seeming discouraging, may be important in the clinical practice, since it indicates that the host immune system is able to control the presence of an allogeneic cell, avoiding undesired proliferation and malignancy. On the other hand, the presence of the cell during a minimum period is necessary, in order to provide therapeutic effects. Second, stem cells are attracted to the site of inflammation by agents such as stromal cell-derived factor (SDF), monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein (MIP-1α) (Park et al., 2009b). Third, undifferentiated cells survive longer and migrate farther in the host tissue than previously differentiated cells (Le Belle et al., 2004). Finally, some tissues secrete differentiation stimulating factors, which could be effective in vivo, avoiding the necessity of previous differentiation (Fujiwara et al., 2004).

Although a significant number of recent studies investigate the therapeutic effects of mature or differentiated cells, it is evident that more immature cell lines also have their advantages. Less differentiated cells maintain stem cell markers, including the stem cell factor receptor, which aid in migration to the sites of injury (Sun et al., 2004). Second, these cells usually have more differentiating potential, compared to the already committed predifferentiated cells (Park et al., 2009a). This property may allow the differentiation of the transplanted cells into more than one cell type, in response to the cytokine and chemokine profile determined by the injured tissue and, therefore, provide better repair. Finally, more immature cell types are usually able to secrete a wider range of growth factors, which are also imperative for tissue regeneration. In fact, although predifferentiated cells may seem functional in vitro, some studies in vivo fail to detect integration with the local cells, even when they maintain expression of the differentiation markers, suggesting that their restorative results are mostly mediated by paracrine effects on endogenous precursors (Ourednik et al., 2002; Yasuhara et al., 2006). Q7

On the other end of the spectrum of the stem cell maturity, the embryonic stem cells combine high differentiation potential, ability to migrate to inflammatory sites, secretion of trophic factors and reduced immunogenicity (Daar et al., 2004). However, major difficulties, associated to uncontrolled cell proliferation and the risk of malignancy have hindered research using those cells. Because of ethical and safety reasons associated with embryonic stem cells, the last decade has witnessed the wide use of adult stem cells as graft source for cell therapy. In the United States, the previous government moratorium on the use of embryonic stem cells also arguably influenced the shift of cell-based therapies towards the use of adult Q8 stem cells (Table 1).

Once defined that adult undifferentiated cells are the main tools, the following step is to determine the optimal source of

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Table 1
Sources of cells for stroke therapy.[a]

Source		References
Adult tissues	Bone marrow	Wu et al. (2008b)
	Umbilical cord blood	Chen et al. (2001), Borlongan (2004)
	Adipose tissue	Leu (2010)
	Amniotic fluid	Rehni et al. (2007)
	Menstrual blood	Borlongan (2010)
	Endogenous neural progenitors	Erlandsson et al. (2010)
	Induced pluripotent stem cells	Jiang et al. (2011)
Embryonic tissue	Embryonic stem cells	Takagi (2005)
	Embryonic or fetal neural tissue	Jin (2005)
	Immortalized neural stem cell cultures	Borlongan and Tajima (1998)

[a] Adult and embryonic tissues comprise possible sources of cells for stroke therapy. Cells derived from adult tissues present a more mature behavior and are more committed to the original tissue. Nevertheless, studies demonstrate cell migration, repair and functional improvement. Embryonic-derived cells, on the other end, have higher differentiation potential, enabling possible cell replacement, but lack proliferative control and are considered unsafe for clinical application.

these cells. For decades, the bone marrow has been used as the stem cell reservoir for diverse types of therapy. In this context, most of the knowledge derives from bone marrow transplantation. In the late years, however, new sources of stem cells have been investigated, as an attempt to avoid the hurdles associated to hematopoietic stem cell harvesting. Moreover, bone marrow-derived cells may have their proliferative potential impaired by aging, smoking and chronic illnesses, such as diabetes mellitus and hypertension, conditions very frequently associated to neurovascular disorders (Umemura et al., 2008; Wagner et al., 2009; Tan et al., 2010; Govaert et al., 2009). Opportunely, some disposable tissues, such as the umbilical cord blood, placenta, amniotic fluid and, more recently, the menstrual blood, have provided less mature cells than the bone marrow, some of which expressing embryonic-like markers (Antonucci et al., 2010; Patel et al., 2008).

Concerning the inflammatory environment of stroke and other neurological disorders accompanied by a significant inflammatory response, a key feature of stem cells is the ability to modulate the immune response, suppressing deleterious mechanisms without affecting beneficial functions. These unique properties are based on the fact that the suppressive capacity of the stem cells is also regulated by the inflammatory environment. In that way, stem cells are able to control the further generation of pro-inflammatory events and therefore limit the progression of the inflammatory response. Neural stem cells, for example, decrease the expression of TNF-α and, in consequence, reduce neutrophil infiltration into the CNS of rat models of hemorrhagic stroke (Lee et al., 2008). Later in the course of inflammation, stem cells also suppress reactive lymphocytes, while enhancing the activity and proliferation of their beneficial, regulatory subsets (Kim et al., 2009). Moreover, trophic factors secreted by the stem cells stimulate angiogenesis and repair (Priya and McDevitt, 2010). Stem cells are, therefore, a very powerful therapeutic tool that still requires further studies to be properly applied with healing purposes. Their potential effects on either acute or chronic inflammatory settings make them useful not only as treatment for stroke, but also for other neurodegenerative conditions in which inflammation is present.

5. The therapeutic potential of stem cells in stroke

Stem cell therapy was been firstly applied to basal ganglia disorders, such as Parkinson's and Huntington's disease, in which inflammation is a chronic feature and tissue repair or replacement is necessary. As stroke is also a basal ganglia disorder and shares several pathophysiological events with the above-mentioned diseases, stem cells seem the ideal therapeutic tool. To date, numerous studies using stem cells for experimental stroke have been published (Borlongan et al., 2004; Felfly et al., 2010; Leu et al., 2010) and their beneficial effects are becoming well established.

Diverse sources of stem cells, with variable degrees of cell differentiation, and different suppressive and regenerative potentials have been used for stroke. Bone marrow-derived cells are the most frequently studied, because of the extensive previous knowledge from bone marrow transplantation for hematologic diseases. The hematopoietic and non-hematopoietic fractions of cells available within the bone marrow have both been applied in experimental studies. Bone marrow-derived cells enriched with hematopoietic precursors injected intravenously enhanced survival of mice with lethal stroke induced by middle cerebral artery ligation (Felfly et al., 2010). Similarly, bone marrow cells injected after stroke induction decreased the size of the ischemic injury in animal models of induced stroke and improved functional recovery (Keimpema et al., 2009; Schwarting et al., 2008). Mesenchymal bone marrow cells prevent neuronal apoptosis and stimulate endogenous repair and angiogenesis, thus improving survival and neurological outcome (Wu et al., 2008a). The mesenchymal cells have also been cultured and differentiated in vitro into neuronal-marker expressing cells, and when injected in animal models of stroke, decreased the size of the ischemic injury and improved neurobehavioral outcome (Koh et al., 2008).

Neural stem cells are also investigated as a promising source of repair, based on the observations that endogenous neural progenitors proliferate after cerebral ischemia. Attempts to stimulate endogenous neurogenesis in ischemic brains include growth factors, anti-inflammatory drugs, Galectin-1, Substance-P, nitric oxide, among others (Liu et al., 2009). Exogenous transplantation of immortalized neural stem cells has improved the outcome of rodents with induced stroke. Borlongan et al. (1998b) reported functional and histopathological improvement of ischemic stroke in rats, after the transplantation of the NT2N lineage of immortalized human neural cells. Neural progenitor cells, obtained from embryonic and fetal tissue, are very effective in the experimental setting. Ischemic rodents transplanted with the cells present a significant reduction of the infarct volume, which correlates to behavioral improvement (Jin et al., 2005). Clinical application of these cells, however, is hampered by the little availability of donor tissues.

Embryonic cells provide the most exciting results, due to the extensive pluripotentiality of these cells. Unfortunately, due to their lack of adequate proliferative control and potential teratogenicity, some investigators have been using in vitro differentiated cells into neuronal progenitors, enabling a safer application. When injected into injured brain sites of rodents, the embryonic stem cells promoted transdifferentiation into neural and neuronal cell types, which were functionally active and improved neurological outcome (Takagi et al., 2005).

The application of stem cells in stroke, although successful in several studies, is criticized because their exact targets and mechanisms of action are still unknown and need investigation. However, evidence shows that they can be effective through multiple pathways, all leading to improvement of the injury. Their lack of specificity may be, then, their best quality. The knowledge about the mechanisms of action of stem cells in stroke is still incomplete and fragmented. Taguchi et al. (2004) suggested an angiogenic effect of CD34+ cells from umbilical cord blood on the ischemic area of stroke. They observed that the cells injected systemically into a mouse model of stroke secreted growth factors (VEGF, FGF2 and IGF-1), induced formation of vascular channels and, secondarily,

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promoted the migration of neuronal precursors into the injured areas, which differentiated and improved nervous function. The addition of anti-angiogenic agents abolished the beneficial effect of the cells, demonstrating the importance of vessels in nervous repair. The issue was later discussed by Saghatelyan (2009), which supported the hypothesis that vasculature-guided neuronal migration can be observed not only following stroke, but also as part of the normal brain development. More recently, endothelial progenitor cells injected into de systemic circulation of mice migrated to the stroke area, promoted repair and improved behavior, in comparison to controls, reinforcing the importance of angiogenesis (Fan et al., 2010). Finally, Nakagomi et al. (2009) demonstrated that the addition of endothelial precursors to neural stem cells, engrafted in mouse models of brain ischemia, enhanced cell survival, proliferation and differentiation, when compared to injections of neural stem cells alone.

In the same study published by Taguchi et al. the authors reported that CD34− cells were not able to promote tissue repair after stroke. Boltze et al. (2008) refuted this last idea through a study in which CD34+ and CD34− cell populations from umbilical cord blood were injected intravenously and had equivalent effects on rat models of stroke. In particular, both cell subtypes promoted functional improvement and migrated to the area of injury, although differentiation into neural markers-expressing cells was not detected. The authors hypothesize that CD133+ CD34− cells might have a role in tissue repair equally as CD34+ cells. This type of discrepant results, although may be construed as hindering the progress of cell therapy, actually exemplifies that the field is maturing and that there is a healthy atmosphere among stem cell researchers to confirm, refute and validate efficacy and safety data. In the end, such rigorous preclinical studies will benefit the transplant recipient.

Until recently, it was believed that cell effectiveness would be conditional on their migration to the site of injury. In fact, several authors observed a direct relationship between cell migration to the site of injury and behavioral improvement (Barzilay et al., 2006; Jin et al., 2005). However, Borlongan et al. (2004) observed, in rat models of stroke, that umbilical cord blood cells were able to promote repair even when not detected in the tissue, probably through the production of growth factors, cytokines and other therapeutic molecules that were able to reach the target. Adding importance to that idea, spanning more than 15 years, considerable research has studied the effect of neurotrophic agents on stroke, as it happened in basal ganglia disorders. Neurotrophic agents influence cell survival, proliferation, differentiation, function and plasticity (Hefti, 1997; Loughlin et al., 1993). They also have a role in physiological endogenous repair, and increased levels can be detected in injured neuronal sites (Connor and Dragunow, 1998). They protect neurons from the cytotoxic insults generated during inflammation, with anti-excitotoxic and anti-oxidant functions, besides improving mitochondrial function.

Administration of agents with specific angiogenic functions, such as vascular-endothelial growth factor (VEGF), angiopoietins, factors that influence Notch signaling, among others, have generated interesting results in neural support (Alexi et al., 2000; Androutsellis-Theotokis et al., 2010; Arboleda-Velasquez et al., 2008). Additionally, some studies have addressed the use of genetically modified cells to release neurotrophic factors at the site of injury. The cells would be used as vehicles, attracted to the inflammatory area of stroke, and the growth factors would provide support to neuronal progenitors, besides promoting angiogenesis in the brain (Maurer et al., 2007). Neurotrophic agents are considered promising for stroke therapy, but their stable and long-term effectiveness still warrants additional investigations, owing in part technical problems related to the manufacturing production of these molecules at clinically therapeutic doses. The combination of neurotrophic factor treatment with cell therapy seems interesting and perhaps will provide exciting results in the future.

6. Other basal ganglia disorders: Parkinson's and Huntington's disease

Experimental stroke studies share overlapping research themes with other animal models of basal ganglia disorders, mainly Parkinson's disease and Huntington's disease, in which numerous therapeutic strategies have been described, aiming to improve survival of remaining neurons, abrogate the ongoing neurotoxic processes or functionally replace the destroyed tissue (Alexi et al., 2000). Cell-based therapy is considered promising and different cell types have been used. Fetal neural tissue, neuronal stem and progenitor cells, tissue engineered to secrete neurotransmitters or neurotrophic factors, para-neuronal cells which support neurons and grafts that may assist the reconstruction of injured axonal pathways have been documented in the literature, with variable results. A major long-standing conundrum in cell therapy is finding the most optimal donor cells. While the more differentiated cells have been thought to offer tissue specific-transplant regimen tailored to treat the specific diseases, their mature phenotype (albeit also mature immune system) renders them to be immunologically rejected by the host and, therefore, rapidly eliminated. On the other hand, less differentiated cells such as the embryonic stem cells are also attractive, since they are better tolerated by the host immune system and have more plasticity, but the risk of uncontrolled proliferation and tumor formation strongly limits their applications.

Parkinson's disease is a common neurodegenerative disease that affects about 2% of the population over 65 years of age. Tremor, rigidity and hypokinesia are caused by a progressive loss of the dopamine-producing neurons from the midbrain substantia nigra, that project into the striatum. Experimental studies have been conducted for approximately 30 years, with exciting data from cell-based therapies, despite some major hurdles (Björklund and Cenci, 2010; Björklund and Lindvall, 2000). The best results were achieved with transplantation of fetal mesencephalic tissue into the striatum, which is the target for dopamine action. In humans, transplantation for Parkinson's disease has been reported since 1982, with initially exciting and later disappointing results (Björklund et al., 1981; Lindvall et al., 1989; Madrazo et al., 1990). The major barrier observed was poor survival of adult grafts in the host brain, which was to some extent solved with the use of tissue from embryonic origin. Still, it is estimated that only about 10% of the transplanted cells survive in the host tissue (Hagell and Brundin, 2001). Fetal mesencephalic tissue has been used to replace the lost neurons and restore dopamine production and comprises an important progress in the field. To date, between 300 and 400 patients have already been grafted with the fetal mesencephalic tissue, but while some report outstanding outcomes, with some patients leaving medication, others fail to observe major effects (Arenas, 2010). The inconsistency of results, ascribed to ethical concerns, limited tissue availability, emergence of unexpected dyskinesias and high rates of graft rejection, still hamper the application of this therapy and stimulate the search for alternatives.

Huntington's disease is genetically determined, with progressive neurodegeneration primarily of the striatum, inducing motor and psychiatric dysfunctions. As in Parkinson's disease, several attempts to delay the progression of the disease have been studied. Treatment of Huntington's disease, though, is complex and requires more than simple neurotransmitter replacement, in that reestablishment of the striatal network is needed. Transplantation of fetal striatal tissue proved to be effective in experimental models of the disease, with symptomatic improvement and evidence of graft incorporation, however controversial establishment of connections with the host striatum remains to be resolved (Borlongan

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et al., 1998a, 1999; Guzman et al., 1999). Clinical trials have been conducted with modest results (Lindvall and Björklund, 2000).

In evaluating the progress of cell therapy for Parkinson's and Huntington's diseases, it is evident that there are technical disparities among the centers that might influence the results and some guidelines are to be determined. Age of the patient, disease stage, number of cells, surgical technique to implant the cells, tissue conservation, among others, are reported as parameters to be defined. Moreover, neurotrophic factors promote neuroprotection, which is essential in both diseases, and some authors propose to combine their use with the transplanted cells (Alexi et al., 2000). Other strategies, using anti-oxidant, anti-excitotoxic, bioenergetic, immunosuppressants and anti-apoptotic agents are also suggested either as stand-alone monotherapy or as adjunct to cell transplantation.

Today, besides the satisfactory results obtained with the transplanted fetal tissue, there is a continued search for other cell sources aiming to treat Parkinson's and Huntingtons's diseases. Little availability of the embryonic tissue is the main reason. Recently, a clinical trial conducted in India tested mesenchymal cells for Parkinson's disease, but while safety was established, efficacy could not be evaluated due to the study design (Venkataramana et al., 2010). Similarly, rat models of Huntington's disease were treated with mesenchymal cells genetically modified to express growth factors, evolving with delay of disease progression (Dey et al., 2010). Other researchers focus on neural tissue differentiated from human embryonic stem cells, but the studies are still in the experimental level, mainly because of safety reasons. These cells, even after differentiation, retain the capacity to form tumors and attempts to reverse it have decreased their survival (Friling et al., 2009; Roy et al., 2006). Finally, there is recent effort in treating Parkinson's disease with autologous induced pluripotent stem cells (iPS), which are interesting for their adult cell origin, avoiding ethical issues. Their safety, however, remains questionable, since formation of neural overgrowths was observed in rats transplanted with these cells, similarly to what was seen with embryonic stem cells (Wernig et al., 2008), likely owing to the lack of regulatory mechanisms in controlling the "stemness" technology employed to revert these mature cells into their undifferentiated plastic state.

In summary, several cell-based studies are being investigated for basal ganglia disorders, mainly using cells already differentiated into neural tissue (Barzilay et al., 2006; Fricker-Gates and Gates, 2010). While it is still early to apply them in clinical trials, at least in large scales, much of the knowledge acquired from experimental studies can be transposed to the treatment of other diseases. Stroke, for instance, is also considered a basal ganglia disease and cell therapy has been extensively applied to it.

7. The search for the optimal donor cell for transplantation

Stem cells have been applied in clinical and experimental research, aiming to improve the outcome of several neurological diseases, either traumatic, neurodegenerative, vascular or autoimmune. Tables 2 and 3 summarize the main therapeutic strategies using stem cells for central nervous system disorders. Most studies investigate local delivery of less mature cell sources (embryonic/fetal tissue), as treatment for Parkinson's and Huntington's diseases, since long-term graft survival is necessary to provide functional replacement. For diseases in which inflammation has a more pronounced role, such as stroke, multiple sclerosis, and probably ALS, adult stem cell sources are mostly used, aiming to modulate the inflammatory response. Mesenchymal cells have immunomodulatory properties and can also be differentiated into specialized cell types or be manipulated by genetic engineering prior to delivery, acquiring a more specific function. In the clinical setting, most studies use bone marrow-derived cells, except for Parkinson's and Huntington's diseases, in which research with fetal neural tissue has been developed for a many years. The diversity of cell sources used in the experimental studies and the their paucity of clinical applications, as can be observed by the numeric disparity between Tables 2 and 3, indicates that further search for a more adequate cell type is still required.

Despite the multiple ongoing studies involving stem cells in CNS disorders, a long-standing challenge in cell therapy is to find the perfect cell graft, which should be immature enough to hold multipotential differentiation properties and yet safe to not induce malignancy. It should also modulate the immune system, decreasing destructive aggression but preserving its ability to fight pathogens. Finally, it should be able to induce changes in the targeted tissue, either restoring its function or promoting repair. Several cell types match the above criteria and have been applied in experimental and clinical research, however, in most cases, ethical and practical issues are a concern. Stem cells from bone marrow, for instance, work well on most studies, but cell harvesting through bone marrow aspiration or leucoapheresis is needed and, the number of cells obtained may be not enough, besides the need of HLA matching. Other sources, like the liver, skin, heart or even induced pluripotent stem cells (iPS), are also available but the isolation and culture of those cells is currently costly and technically complicated (Gerbal-Chaloin et al., 2010; Huang et al., 2010; Mosna et al., 2010). There is interest, therefore, in acquiring stem cells from disposable and easily accessible tissues, such as the amnion and amniotic fluid, placenta, adipose tissue and, more recently, menstrual blood.

8. Stem cells derived from the endometrium: characterization and applications

The presence of stem cells in the endometrium was described about 30 years ago, from the observation that the upper layers of this tissue shed and were renovated each month (Padykula, 1991; Prianishnikov, 1978). The original notion then, however, stipulates that stem cells were intact in the endometrium but that all cells from the functionalis layer shed in the menstrual were non-viable nature. Epithelial cells compose part of the endometrium, and are found in the surface epithelium and in the tubular glands, which extend from the surface to the interface with the myometrium. The rest of the endometrium consists of stromal cells, smooth muscle cells, endothelial cells and leukocytes (Padykula, 1991). Functionally, the endometrium can be divided in two main layers. The upper layer, named functionalis, contains mostly glands loosely held together by stromal tissue, while the lower layer, basalis, contains dense stroma and branching glands. The funcionalis is eliminated monthly, as menstruation, and the basalis persists and gives rise to the new endometrium, under hormonal influence.

Only in the last few years, have endometrial cells been better characterized. Chan et al. (2004), reported epithelial and stromal cells that were isolated from the endometrium and cultured in vitro. Both were clonogenic and proliferated in laboratory, but the epithelial cells lost part of their phenotypic markers and needed a feeder layer as the cultures progressed. Meng et al. (2007) published a study with stem cells obtained from the menstrual blood, which showed similar properties. The cells were differentiated into tissues from the three germ layers, indicating their multipotentiality in vitro, and therefore were named endometrial regenerative cells (ERC). Shortly after, Patel et al. (2008) published a more complete study, in which stromal stem cells, again isolated from menstrual blood (MenSCs), were expanded in vitro, and showed clonogenic properties and ability to differentiate into mesoderm and ectoderm derived-tissues. They also demonstrated that the MenSCs expressed markers of pluripotency, such as Oct-4, SSEA-4 and c-kit,

Please cite this article in press as: Rodrigues, M.C.O., et al., Recent progress in cell therapy for basal ganglia disorders with emphasis on menstrual blood transplantation in stroke. Neurosci. Biobehav. Rev. (2011), doi:10.1016/j.neubiorev.2011.05.010

Table 2
Experimental cell-based therapy for central nervous system disorders.[a]

	Disease	Donor cells	Injection site	References
	Stroke	Human umbilical cord blood cells	IV[b] or local	Chen et al. (2001), Borlongan (2004)
		Endogenous neural progenitor and stem cells	Mobilization with CSA[c]	Erlandsson et al. (2010)
		Immortalized neural stem cells from culture	Local	Borlongan and Tajima (1998)
		Differentiated embryonic stem cells	Local	Takagi (2005)
		Neural progenitor cells from fetal tissue	Local and IV	Jin (2005)
		Mesenchymal cells from bone marrow	IV	Wu et al. (2008b)
		Menstrual blood stem cells	IV or local	Borlongan (2010)
		Mesenchymal cells from adipose tissue	Local	Leu (2010), Ikegame (2011)
Q31	Multiple sclerosis	Neural precursor/stem cells	ICV[d]; IV; IV and IT[e]	Einstein et al. (2009), Carbajal et al. (2010), Pluchino et al. (2009)
Q32				
Q33		Bone marrow mesenchymal cells	IV	Bai et al. (2009), Rafei et al. (2009)
Q34		Adipose tissue-derived MSC[f]	IV	Constantin et al. (2009)
		Genetically engineered bone marrow stem cells	IV	Makar et al. (2009)
		Genetically engineered MSC	ICV	Barhum et al. (2010)
		Fetal glial cells	Site of demyelination	Gout and Dubois-Dalcq (1993)
Q35	Parkinson's disease	Genetically engineered MSC	Striatum	Shi et al. (2010), Somoza et al. (2010)
Q36		Neural stem cells differentiated from ESC[g]	Striatum	Yang et al. (2008, 2010a)
Q37		Genetically engineered embryonic stem cells	Striatum	Cui et al. (2010)
Q38		Human umbilical cord tissue neural cells	Striatum	Li et al. (2010b)
		Bone marrow-derived neural stem cells	Striatum	Zou et al. (2010), Glavaski-Joksimovic et al. (2009)
Q39		iPS[h] cells	Striatum	Glavaski-Joksimovic et al. (2010), Xu et al. (2010b)
Q40		Umbilical cord tissue MSC	Striatum	Xiong et al. (2010)
		Human umbilical cord blood cells	IV	Ende and Chen (2002)
Q41		Human endometrium-derived neural cells	Striatum	Wolff (2010)
		Human amniotic epithelial cells	Striatum	Yang et al. (2010b)
		Sertoli cells	Striatum	Borlongan et al. (1997), Sanberg et al. (1997)
Q42				
Q43	Huntington's disease	Fetal neural tissue	Striatum	Lim et al. (2008)
Q44		Neural stem cells differentiated from ESC	Striatum	Vazey et al. (2010)
Q45		Genetically engineered mesenchymal cells	Striatum	Dey (2010)
Q46		Bone marrow mesenchymal cells	Striatum	Snyder et al. (2010)
		Sertoli cells	Striatum	Rodriguez et al. (2003)
	Alzheimer's disease	Fetal neural tissue	Hippoc[i]; forebrain; cortex	Ryu (2009), Xuan et al. (2009), Wu et al. (2008b)
Q47				
Q48		Bone marrow MSC	IC[j]	Lee et al. (2010)
		Neural stem cells differentiated from ESC	IC	Moghadan et al. (2009)
Q49	Amyotrophic lateral sclerosis	Human umbilical cord blood cells	IV	Garbuzova-Davis et al. (2003, 2008)
		Bone marrow adult c-kit+ stem cells	IV	Corti et al. (2010)
		Adipose tissue-derived stem cells	IV	Gu et al. (2010)
Q50		Neural stem cells	IV; IT	Mitrecic (2010), Hwang et al. (2009)
		Neural cells from teratocarcinoma cell line	Intraspinal	Garbuzova-Davis et al. (2006)
Q51		Mesenchymal cells	ICM[k]; IV	Kim et al. (2010), Vercelli et al. (2008), Zhao et al. (2007)
Q52		Embryonic stem cells	IV	Deshpande et al. (2006)
		Motor neurons differentiated from ESC	Intraspinal	López-González et al. (2009)
		Sertoli cells	Intraspinal	Hemendinger et al. (in press)
	Spinal cord injury	Mesenchymal cells from hUC[l]	Site of injury	Hu et al. (2010)
		Fetal umbilical cord tissue cells	Site of injury	Erdogan et al. (2010)
Q53		Neural cells derived from human ESC	Site of injury	Erceg et al. (2010), Marques et al. (2010)
		Epidermal neural crest stem cells	Site of injury	Sieber-Blum (2010)
Q54		Neural stem cells	Site of injury	Abematsu et al. (2010)
		iPS cells	Site of injury	Tsuji et al. (2010)
Q55		Olfactory ensheating cells	Site of injury	Ramon-Cueto et al. (1998), Jeffery et al. (2005)
		Mesenchymal cells from adipose tissue		Kang (2006), Ryu (2009)

[a] Here are listed most of the available experimental studies on cell therapy for central nervous system disorders. Parkinson's and Huntington's disease focus on local delivery of less mature cell sources (embryonic/fetal tissue), since long-term graft survival is necessary to provide functional replacement. For diseases in which inflammation has a more pronounced role, such as stroke, multiple sclerosis, and probably ALS, adult stem cell sources are mostly used, aiming to modulate the inflammatory response. Mesenchymal cells are an exception, since although adult stem cells, they are usually well tolerated by the host immune system, and have immunomodulatory properties. These cells can also be differentiated into specialized cell types or be manipulated by genetic engineering prior to delivery, acquiring a more specific function.
[b] IV: intravenous cell delivery.
[c] CSA: cyclosporine A.
[d] ICV: intracerebroventricular delivery of cells.
[e] IT: intrathecal delivery of cells.
[f] MSC: mesenchymal stromal cells.
[g] ESC: embryonic stem cells.
[h] iPS: induced pluripotent stem cells.
[i] hippoc: hippocampus.
[j] IC: intracerebral delivery of cells.
[k] ICM: intracisterna magna delivery of cells.
[l] hUC: human umbilical cord.

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Table 3
Clinical stem cell applications for central nervous system disorders.[a]

	Disease		Injection site	References
Q56	Ischemic stroke	Bone marrow mesenchymal stem cells	IV[b]	Bang et al. (2005)
Q57		Bone marrow hematopoietic stem cells	IV	Banerjee (2011)
Q58		NT2N from immortalized cell line	Local	Kondziolka et al. (2000)
Q59	Multiple sclerosis	Bone marrow hematopoietic stem cells	IV	Burt et al. (2009), Fassas et al. (2002), Hamerschlak et al. (2010)
Q60		Bone marrow mesenchymal stem cells	IV	Yamout et al. (2010), Liang et al. (2009)
Q61		Menstrual blood stromal cells	IT[c], IV	Zhong (2009)
Q62	Parkinson's disease	Fetal neural tissue	Striatum	Lindvall (1989), Madrazo (1990)
		Bone marrow mesenchymal cells	SLV[d]	Venkataramana (2010)
Q63	Huntington's disease	Fetal neural tissue	Striatum	Gallina et al. (2010), Capetian et al. (2009)
Q64		Neural cells derived from ESC[e]	Striatum	Aubry et al. (2009)
Q65	ALS[g]	Olfactory ensheating cells (OEC)	IV	Gamez et al. (2010)
		Mesenchymal cells	IV; intraspinal	Gamez et al. (2010), Mazzini et al. (2010)
Q66		Bone marrow stem cells	IV	Appel et al. (2008), Deda et al. (2009)
Q67		Autologous bone marrow stem cells	Mobilization w/G-CSF[f]	Tarella et al. (2010), Nefussy et al. (2010)
Q68		Autologous CD133+ bone marrow cells	Motor cortex	Martinez et al. (2009)
Q69	Spinal cord injury	Mesenchymal bone marrow cell	IT	Kishk et al. (2010)
Q70		Olfactory ensheating cells (autologous)	Site of injury	Feron et al. (2005), Jeffery et al. (2005)

[a] List of most of the available clinical applications of stem cells for the treatment of central nervous system disorders.
[b] IV: intravenous cell delivery.
[c] IT: intrathecal cell delivery.
[d] SLV: sublateral ventricular area cell delivery.
[e] ESC: embryonic stem cells.
[f] G-CSF: granulocyte-colony stimulating factor (filgrastim).
[g] ALS: amyotrophic lateral sclerosis.

which are frequently found in more immature cell types, including the embryonic stem cells.

Cervelló et al. (2010) isolated, through flow cytometry of Hoechst-stained endometrium cells, epithelial and stromal cell enriched side populations. The cells were characterized in vitro, and showed a high clonogenic and proliferative potential, especially when exposed to hypoxic conditions, which mimic the endometrial environment. However, when the cells were studied in vivo, injected subcutaneously in immunodeficient mice, they showed limited proliferative and differentiation potentials. Masuda et al. (2010) studied the same side population of cells and conducted similar studies. The cells were implanted under the kidney capsule of female mice and, after estrogen stimulus, human tissue development was observed in few animals. The authors demonstrated the differentiation of the side-population cells into glandular epithelial, stromal and, for the first time, endothelial cells, since small and medium sized vessels co-expressing CD31 and human vimentin were observed. Although detectable, their differentiation capacity in vivo was considered poor and better proliferative results were obtained when the cells were combined with the remaining population (main population) of endometrial cells. These findings, taken together with existing data from literature, suggest that a multiple factors derived from the endometrium, instead of a single cell type, cooperate for the therapeutic properties of this tissue.

That stem cells derived from menstrual blood can be categorized based on their phenotypic and proliferative properties has been a hotly debated topic. As an example, Murphy et al. (2008) believe that the endometrial regenerative cells (ERC) isolated by them are not the same as the endometrial stromal cells described by Taylor (2004), but may share overlapping properties and may even be equivalent cells as those reported by other studies (Meng et al., 2007; Patel et al., 2008; Wolff et al., 2010). Endometrial regenerative cells, for instance, express low concentrations of the Stro-1 marker and exhibit higher proliferative capacity than other endometrial-derived cells. According to Taylor (2004), stromal cells found in the endometrium originate from the bone marrow, as observed in recipients of allogeneic bone marrow transplantation. The findings were later reproduced in female rats transplanted with GFP bone marrow cells, which presented GFP cells in the endometrium long after transplantation (Bratincsák et al., 2007). In practical matters, however, they seem to have similar effects and comparable therapeutic abilities to promote repair when applied in vivo (Table 4).

The angiogenic potential of the endometrium-derived cells is very relevant for the experimental investigations of vascular growth and remodeling and, perhaps, even for designing clinical therapeutic studies, as these cells might be applied to cardiovascular diseases. In fact, Hida et al. (2008) published their experience with menstrual blood-derived stromal cells in damaged heart tissue, in which they were able to in vitro differentiate the cells into spontaneously beating cardiomyocyte-like cells. When menstrual blood cells were injected in the ischemic tissue of myocardial infarct rat models, functional improvement was noted, differently than what was observed when bone marrow stromal cells were used. Finally, the authors also reported evidences of cell engraftment and transdifferentiation into cardiac tissue. Some authors propose to take advantage of the angiogenic potential of these cells, applying them to the treatment of chronic limb ischemia and, more recently, severe skin burns, using the cells associated to intelligent artificial films (Drago et al., 2010; Murphy et al., 2008).

In the nervous system context, Borlongan et al. (2010), very recently published the results of menstrual blood cell transplantation in experimental stroke. Stromal-like menstrual blood stem cells were isolated, expanded and, at last, selected for CD117, a marker associated with high proliferation, migration and survival (Cho et al., 2004). In vitro studies showed that the expanded cells maintained expression of embryonic-like stem cell phenotypic markers, such as Oct-4, SSEA-4 and Nanog, even when cultured up to nine passages, as an evidence of the safety and reliability of these cells, and some were induced to express neural markers (MAP2 and Nestin). Moreover, when added to culture rat neurons exposed to a hypoxic insult, the menstrual blood cells provided neuroprotection and when applied to rat stroke models, less neurologic deficit was observed on behavioral tests, irrespective of the injection site, *i.e.* systemic or local administration into the striatum. However, analysis of the tissue, after animal sacrifice, revealed that although

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Table 4
Evolution of endometrial/menstrual blood stem cells investigations.[a]

Year	Event	Reference
1978	First description of stem cells in the endometrial tissue based on the observations of the monthly tissue shedding	Prianishnikov (1978)
1991	Supports the idea of stem cells in the endometrial tissue based on the potential of the endometrial cells to migrate and generate new tissue in endometriosis	Padykula (1991)
2004	Isolation and culture of epithelial and stromal cells from the endometrium. Observed clonogenicity and in vitro proliferation	Chan et al. (2004)
2007	Isolation and culture of cells from menstrual blood, similar to cells isolated from the endometrium. Differentiation into the three germ layers	Meng et al. (2007)
2007	Intramuscular application of human endometrial and menstrual blood-derived cells in a murine model of Duchenne muscular dystrophy. In vitro and in vivo demonstration of fusion of injected cells to myoblasts and production of human dystrophin by the treated muscle	Cui et al. (2007)
2008	Isolation, culture and differentiation of menstrual blood stromal cells into mesodermal and ectodermal tissues. Expression of markers of immature cell types	Patel et al. (2008)
2008	Differentiation of menstrual blood stromal cells into spontaneously beating cardiomyocytes in vitro. Functional improvement of myocardial infarct rat models and in vivo evidence of cell engraftment and differentiation	Hida et al. (2008)
2009	Safety study of intravenous/intrathecal administration of endometrium-derived stromal cells in refractory multiple sclerosis patients. No adverse effects observed. Clinical stabilization in short follow-up period	Zhong et al. (2009)
2010	Menstrual blood stromal cells expressed neural markers in vitro. Neuroprotection of neural tissue cultures when menstrual blood cells were added. Functional improvement of rat model of stroke, with migration of cells to the site of injury, but without evidence of cell differentiation	Borlongan et al. (2010)
2010	Endometrial-derived stem cells injected in a rat model of Parkinson's disease. Evidence of migration, engraftment and differentiation, along with increased concentrations of striatal dopamine	Wolff et al. (2010)

[a] List of the publications on endometrium-derived stem cells, from the first report of the existence of stem cells in such tissue, to the clinical applications of these cells.

human cells were detected in the rat brain, some migrating to areas other than the injected, they did not show signs of differentiation, expressing their original markers. Once more, there is evidence that cell differentiation is not the main pathway of neuroprotection or neuroregeneration.

Wolff et al. (2010) reported the use of endometrial-derived neural cells in a Parkinson's disease mouse model. Endometrial-derived stromal cells were differentiated in vitro into dopamine-producing cells, and then engrafted into the brain of the animals. Migration, differentiation and production of dopamine were detected in vivo, demonstrating the therapeutic potential of these cells to functionally restore the damaged tissue, either through cell replacement or endogenous repair.

The only clinical study yet published evaluated the safety aspects of endometrial-derived stromal cells administration (Zhong et al., 2009). Four patients with multiple sclerosis were treated with intrathecal injections of 16–30 million cells and one of the patients also received an additional intravenous injection. No adverse events were registered, as expected, and the authors reported functional stabilization. However, the longest follow-up reached 12 months, and any conclusions about effectiveness of the treatment seem premature in this long-term and slowly progressive illness.

Taken together, the available evidence regarding menstrual blood-derived cells favor their future application in clinical studies. In comparison to stem cells from other sources, especially those from the bone marrow, menstrual blood-derived stem cells have the advantage of presenting a more immature phenotype, through the expression of embryonic-like surface markers. Their immature behavior is confirmed by in vitro differentiation studies, in which menstrual blood-derived cells give rise to diverse tissue types from all three germ layers (Patel et al., 2008; Meng et al., 2007). Moreover, they seem to have a higher proliferative capacity, above 30 population doublings, when compared to stromal cells from other sources, such as the bone marrow and dental pulp, which are limited to approximately 20 population doublings (Gargett et al., 2009). Additionally, cultured menstrual blood cells maintain longer telomerase activity than bone marrow-derived cells (Patel et al., 2008). These observations may reflect higher regenerative and differentiation potentials in vivo, yet to be confirmed by comparative studies between stromal cells from different sources.

Strong competitors to menstrual blood cells are the adipose tissue MSC, lately investigated as alternatives to bone marrow MSC. These cells present high proliferative capacity and angiogenic potential possibly through expression of VEGF and hepatocyte growth factor (HGF). Experimental models of chronic myocardial infarction (Mazo et al., 2008), limb ischemia (Moon et al., 2006; Nakagami et al., 2005), stroke (Leu et al., 2010; Ikegame et al., 2011), spinal cord injury (Kang et al., 2006; Ryu et al., 2009) and retinal lesions (Xuqian et al., 2011), among others, have shown optimistic results about the regenerative potential of adipose tissue cells. The few human studies available establish safety of these cells and reproduce the animal outcomes (Poliachenko et al., 2010; Ra et al., 2011). In vitro studies, however, have revealed high proliferative rates, but with conflicting results regarding senescence (Gargett et al., 2009; Kern et al., 2006). Comparative evaluations among cells from different sources, especially concerning disposable tissues, are necessary to effectively determine which is the best cell type. In the future, better understanding the properties and mechanistic pathways may allow the cell types to be chosen according to their application. Meanwhile, abundance, frequency and expansion potential of the cells seem to be important criteria in establishing the best cell source (Kern et al., 2006). In this sense, menstrual blood and adipose tissue cells may be equivalent, the former bearing the advantage of dispensing any invasive procedure to be collected, and the latter of being available in both sexes.

9. Limitations and practical issues

Menstrual cells are a novel therapeutic option in this field and have great potential, as already demonstrated through experimental studies. In the clinic, the application of autologous stem cells derived from menstrual blood would be ideal to avoid graft rejection issues. However, the low yield and difficulty in expansion of ample supply of stem cells from this source is a barrier to be transposed. Although presenting high proliferation rates, the cells require time to multiply and achieve sufficient quantities for clinical applications, therefore limiting autologous use. Moreover, this approach would be restricted to the female population. Males and post-menopausal women, which are the main targets of stroke and neurodegenerative diseases, would be excluded from the therapy. A feasible solution would be to educate the female pre-menopausal population about the potential of the menstrual cells and, therefore, stimulate the anticipated harvesting and cryopreservation of the cells, for future autologous use. For the male population, however, there remain the options of using allogeneic menstrual blood

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cells and of searching for an alternative source of cells or a male counterpart cell.

An ideal scenario would be a woman, affected by a stroke, with autologous menstrual blood-derived cells previously collected, expanded up to third passage and cryopreserved. In a few days these cells would be thawed, further expanded if necessary, and available for intravenous delivery in adequate time for their best effectiveness in the rescue of the penumbra area. In a more realistic setting, the patient would be a man or a woman without stored cells and lacking enough time for harvesting and expansion. These would still benefit from the use of allogeneic cells which, being stromal cells, present low immunogenicity and, therefore, tolerable rejection rates. Similar approaches would be reasonable for Parkinson's disease, since women are mostly affected after menopause. For Huntington's disease, gene screening would allow the female carrier the opportunity of autologous cell storage before onset of symptoms.

For a stroke-affected patient, the slightest improvement in neurological function can be decisive for self-sufficiency and, even, for ability to work, which are ultimately translated into financial independence. Therefore, investing in cell banking as a safety measure against possible future events may be a wise and even profitable step. While cell banking is already widely accessible for umbilical cord blood, only recently has it also become available for menstrual blood cells and, yet, limited to autologous or, at most, familiar use. It is possible, however, to expand the availability of menstrual blood cells to a wider population of allogeneic recipients. Women in child-bearing age may donate samples of menstrual blood, enabling storage of multiple HLA-typed cells for future use. As a further possibility, the cells could be expanded and differentiated into specific tissues and be ready for eventual use (Zhang et al., 2009). An efficient banking system for menstrual blood cells would require an organized and updated registration system, enabling prompt localization and rapid retrieval of the cryopreserved cells, just in time for therapeutic use.

Cell banking for human use requires precautions to warrant safety and effectiveness of the expanded and stored cells. Cell cultures should be continuously surveilled, not only for proliferation and signs of senescence, but also for viability, phenotypic and morphological alterations, microbiological contamination and possible chromosomal disruptions (Sensebé et al., 2011). Therefore, strict GMP-compliant procedures should be formally established before the proliferation of cryopreservation companies for menstrual blood storage, as well as for preservation of cells from other sources.

10. Concluding remarks and future perspectives

Research on cell therapy for stroke has reached great proportions, especially because of the possibility of translational studies, which have already started. Most studies use the knowledge of neuroregenerative areas of the brain, more specifically the hippocampus and, still with some controversy, the subventricular zone to guide their studies, although some have shown cell migration and repair of areas other than those regions considered as exhibiting high neurogenic capacity (Li et al., 2010a; Mezey et al., 2000). Furthermore, it seems clear that the rescue of the penumbra area after stroke is decisive for functional outcome and a great opportunity for cell therapy. Stem cells promote neuroprotection especially through modulation of the activated immune system. Tissue repair is also described and, although cell differentiation is observed in the experimental setting, its importance to the final outcome of the treatment is still undefined.

Menstrual cells combine characteristics that are convenient for clinical application and, in parallel with cells derived from other disposable tissues, may have a role in the future investigations. Despite the potential challenges still to be solved, the menstrual cells represent an important therapeutic tool that may improve the outcome of stroke and other neurodegenerative diseases, and decrease the disability of future patients. Experimental studies should be extended aiming to increase the knowledge about the mechanisms of action of these cells to allow optimization of the cells' therapeutic outcome.

Disclosures

CVB and PRS serve as consultants, and PRS is a co-founder of Saneron-CCEL Therapeutics, Inc., and CVB, PRS, and JGA have a patent application in this area, owned jointly by Cryo-Cell International, Inc. and Saneron-CCEL Therapeutics, Inc. Cryo-Cell International, Inc. provided the foundational menstrual stem cell technology in the patent applications of M.A. Walton and JGA wholly owned by Cryo-Cell International, Inc.

Uncited reference

Rothwell and Luheshi (2000).

Acknowledgement

CVB and SGD are funded by James and Esther King Biomedical Research Program. CVB and PRS have a patent application on menstrual blood stem cells for stroke therapy. CVB, PRS, and SGD are consultants of Saneron-CCEL Therapeutics Inc. The authors express their gratitude to Ms. Cate Bae for technical assistance in the preparation of this manuscript.

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Please cite this article in press as: Rodrigues, M.C.O., et al., Recent progress in cell therapy for basal ganglia disorders with emphasis on menstrual blood transplantation in stroke. Neurosci. Biobehav. Rev. (2011), doi:10.1016/j.neubiorev.2011.05.010

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Please cite this article in press as: Rodrigues, M.C.O., et al., Recent progress in cell therapy for basal ganglia disorders with emphasis on menstrual blood transplantation in stroke. Neurosci. Biobehav. Rev. (2011), doi:10.1016/j.neubiorev.2011.05.010

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Please cite this article in press as: Rodrigues, M.C.O., et al., Recent progress in cell therapy for basal ganglia disorders with emphasis on menstrual blood transplantation in stroke. Neurosci. Biobehav. Rev. (2011), doi:10.1016/j.neubiorev.2011.05.010

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Please cite this article in press as: Rodrigues, M.C.O., et al., Recent progress in cell therapy for basal ganglia disorders with emphasis on menstrual blood transplantation in stroke. Neurosci. Biobehav. Rev. (2011), doi:10.1016/j.neubiorev.2011.05.010