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Stem Cell in Neurological Disorders

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1. Introduction

There are various sources of stem cells which are being studied for their potential in stem cell-based therapies for CNS diseases (Yu D & Silva, 2008):

1.1 Embryonic stem cells

Embryonic stem cells are pluripotent cells with indefinite self-renewal capabilities as well as the ability to differentiate into all cell types derived from the 3 embryonic germ layers (How Embryonic, 2010). Embryonic stem cells are favorable in the research community because they are relatively easy to isolate, can grow indefinitely, and have the potential to develop into any type of adult cell.

1.2 Adult stem cells

Adult stem cells (ASCs) play a critical role in tissue maintenance and repair (Stem Cell Basics, 2010). Research on adult stem cells began in the 1950s with the discovery of multipotent hematopoietic and mesenchymal stem cells in bone marrow, which can generate a number of tissues (Stem Cell Basics, 2010). **Bone Marrow-Derived Mesenchymal Stem Cells** can be expanded and differentiated in vitro using various media formulations and culture surface conditions to direct them to different cell lineages (Ho et al., 2006). BMSCs have the ability to migrate to areas of injury, even crossing the blood-brain barrier (Akiyama et al., 2002; Tang et al., 2007). **Although the reproducibility of BMSC therapies needs to be thoroughly examined, these early experiments suggest that BMSCs can be administered intravenously to CNS targets.** (Rice & Scolding, 2008)

1.3 Neural stem cells

The adult mammalian CNS contains NSCs which were first inferred from evidence of neuronal turnover in the olfactory bulb and hippocampus in the adult. (Altman & Das, 1965, 1966). Neural stem cells are able to differentiate into neurons, astrocytes, oligodendrocytes and various forms of neural precursors (Flax et al., 1998; Gage, 2000; Palmer et al., 1997; Takahashi et al., 1999; Weiss et al., 1996). Moreover, in vivo delivery of these cells to animal models of neurodegenerative diseases was associated with varying degrees of functional recovery (Ourednik et al., 2002). Figure (1) (Lindvall & Kokaia., 2006)

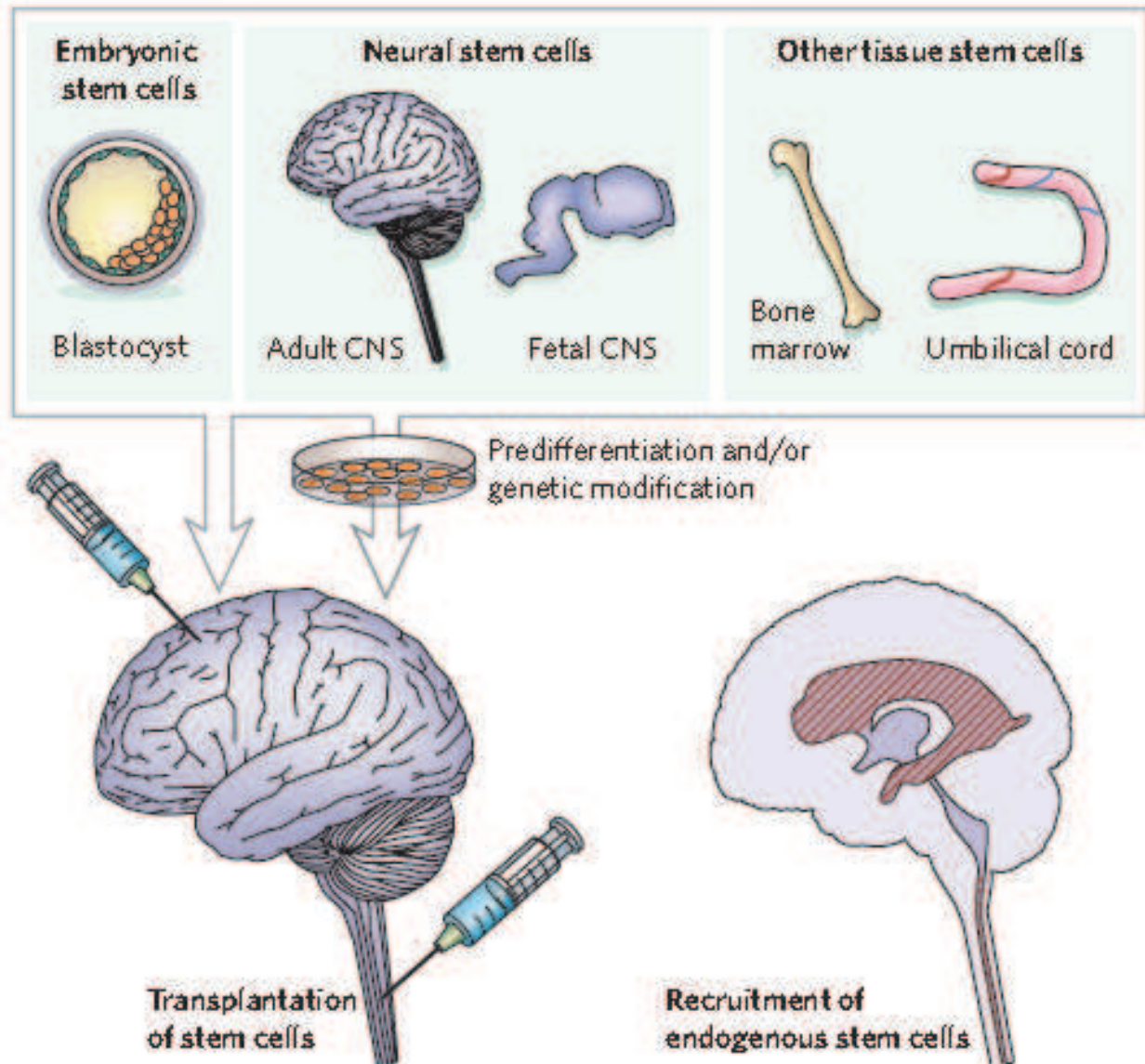


Fig. 1. Application of stem cells for neurological disorders. Stem cells would be isolated and transplanted to the diseased brain and spinal cord, either directly or after predifferentiation/genetic modification in culture to form specific types of neuron and glial cell, or cells producing neuroprotective molecules. In strategies relying on stimulation of the patient's own repair mechanisms, endogenous stem cells would be recruited to areas of the adult brain and spinal cord affected by disease, where they would produce new neurons and glia (neurogenic and gliogenic areas along lateral ventricle and central canal are shown in hatched red). Stem cells could provide clinical benefits by neuronal replacement, remyelination and neuroprotection.

2. Strategies for using stem cells to treat neurological disorders

These include strategies in which:

- i. Stem cells are transplanted within the brain, are infused by blood circulation (Figure 2); or delivered through bone marrow transplantation (BMT; Figure 2).

- ii. Stem cells are stimulated by cytokines, or trophic and growth factors, into the brain in vivo;
- iii. Stem cells are engineered to correct the genetic defect (Figure 2), delivery of therapeutic agents.
- iv. Stem cells are combined with biomaterials (Figure 2).

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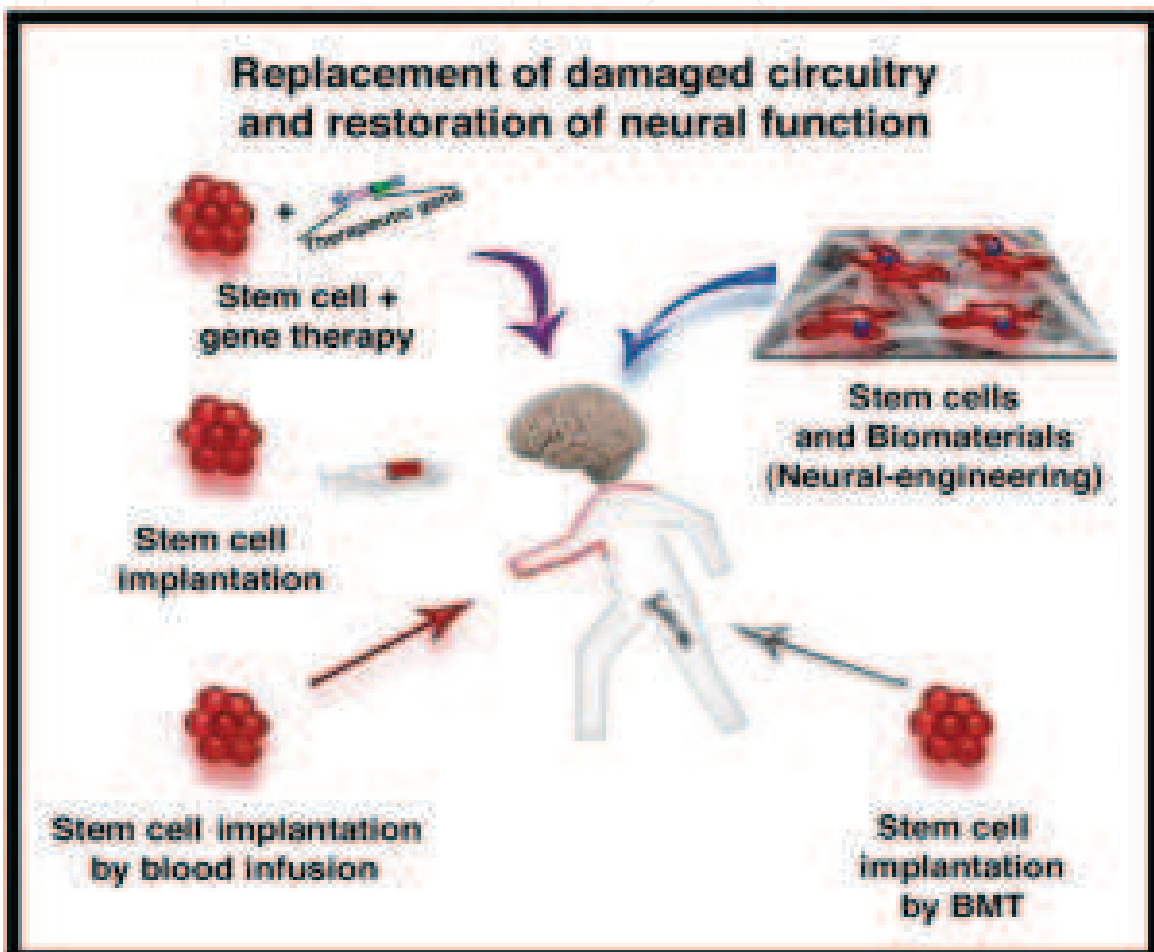


Fig. 2. Stem cells replacement therapy for neurological diseases. Cartoon schematizes the different strategies for stem cell delivery in order to repair the degenerated tissue.

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2.1 Cell replacement through transplantation of exogenous cells

Transplanted donor cells into a host organism offer the chance to expand and manipulate cells in vitro. This method has proven successful in the haematopoietic system. Such method to be successful in the CNS the transplanted cells must (1) survive the transplantation; (2) migrate to the site of replacement; (3) differentiate into appropriate cell phenotype(s); and (4) make appropriate connections with the host tissue.

The condition is further complicated during neurodegenerative disease, since the same factors that cause mature neurons to die (oxidative stress, accumulation of toxic protein aggregates, etc.), may also lead to cell death in transplanted cells. There are a number of

criteria for improving the opportunities for successful cell replacement using transplanted cells. Generally, selecting cells from the same region as the region to which the cells will be transplanted increases the transplantation success rate. (Tobi& Mahendra., 2005)

2.2 Mobilization of endogenous stem cells

A second therapeutic approach is the mobilization of endogenous cells to replace lost or damaged cells. The production of new neurons (neurogenesis) occurs at a very low rate in the adult brain, in two regions: the subventricular zone of the lateral ventricle, which produces new neurons of the olfactory bulb, and in the hippocampus. Neurogenesis can be stimulated in the adult brain by factors, including diet, exercise and modification of hormone levels. (Tobi& Mahendra., 2005)

Moreover, neurogenesis can be stimulated in the adult brain by growth factors, such as epidermal growth factor (EGF) or basic fibroblast growth factor (bFGF). However, delivery of these factors is complicated, since growth factors are large molecules that cannot penetrate the blood-brain barrier when it is intact. Transfer of growth factors into the adult CNS can be accomplished through direct injection into the brain and/or the ventricles within the brain or through transplantation of cells genetically engineered to secrete growth factors into the surrounding environment. Additionally, growth factors can be used to protect endogenous NPCs neural progenitor cells from dying. (Tobi& Mahendra., 2005)

2.3 Delivery of therapeutic agents

Drug Delivery to the CNS is complicated by the blood-brain barrier, which prevents many large, hydrophilic molecules from entering the brain through the bloodstream. One potential use of NPCs neural progenitor cells is as delivery agents for pharmacological compounds. A large number of studies provides evidence that delivery of supportive factors can slow the degeneration process in several neurodegenerative diseases. Although this method has many problems, including controlling the survival rate of transplanted cells and controlling the rate of drug secretion, this is one path currently being explored for therapy using stem cells. (Tobi& Mahendra., 2005)

2.4 Stem cells are combined with biomaterials

Tissue engineering approach includes the transplantation of stem cells in combination with natural or synthetic biomaterials (Dawson et al., 2008). Verification came from data showing that chemical and biological modifications of biomaterials could directly influence stem cell behavior (e.g., change of substrate properties, nanopattern design, scaffold degradation rate) (Atala, 2009; Martino et al., 2009).

3. Stem cells for different neurological disorders

The use of stem cells in neurological diseases is much more complex than in other systems. Many challenges are unique to the nervous system are as follows: (a) The need to integrate into a sophisticated array of interconnected cells that extend over great distances; (b) The absence of developmental cues in adults that guided the establishment of neural networks during development, thus making regeneration more difficult; (c) The possibility in progressive or recurrent neurologic diseases that the transplanted cells may be attacked and injured (Potter et al, 2007)

3.1 Parkinson's disease

A widespread loss of dopamine neurons (DA) in the substantia nigra pars compacta and their terminals in the striatum occurs in Parkinson's disease (PD) (Kish et al., 1988; Agid, 1991). Many issues for the dopaminergic depletion associated with the disease have been suggested, including programmed cell death, viral infection, and environmental toxins. As an efficient treatment for PD, patients have been given L-dihydroxyphenyl alanine (L-DOPA), a precursor of dopamine, but long-term administration of L-DOPA consequently produces side effects (Lang and Lozano, 1998 a, b). So, human fetal ventral mesencephalic tissues were transplanted into the striatum of PD patients as a successful therapy for patients with advanced disease, since the late 1980s (Lindvall et al., 1990; Olanow et al., 1996; Kordower et al., 1997; Dunnett and Bjorklund, 1999). This fetal tissue transplantation has serious problems associated with ethical and religious questions and logistics of acquiring fetal tissues (Hagell et al., 1999). To avoid these difficulties, utilization of neurons with a DA phenotype generated from ESCs, MSCs, or NSCs could serve as a practical and effective alternative for fetal brain tissues for transplantation. DA neurons were generated from mouse ESCs or mouse NSCs (Lee et al., 2000; Hagell & Brundin, 2002; J.H. Kim et al., 2002; T.E. Kim et al., 2003). Neural cells with a DA phenotype have been generated from monkey ESCs by coculturing with mouse bone marrow stromal cells (Takagi et al., 2005) and also from human NSCs derived from fetal brain (Redmond et al., 2007), and improvement was seen in MPTP lesioned monkeys following intrastriatal transplantation of these cells (Takagi et al., 2005; Redmond et al., 2007).

NSCs which were transplanted in the brain attenuate anatomic or functional deficits associated with injury or disease in the CNS via cell replacement, release of specific neurotransmitters, and production of neurotrophic factors that protect injured neurons and promote neuronal growth. Recently, continuously dividing immortalized cell lines of human NSC have been generated from fetal human brain cell culture via a retroviral vector (Kim, 2004; Lee et al., 2007; Kim et al., 2008), and one of the immortalized NSC lines, induced functional improvement in a rat model of PD following transplantation into the striatum (Yasuhara et al., 2006).

3.2 Alzheimer's disease

Alzheimer disease is characterized by degeneration and loss of neurons and synapses throughout the brain, particularly in the basal forebrain, amygdala, hippocampus, and cortical area. Cognitive function of patients progressively declines, and patients become demented and die prematurely (Coyle et al., 1983). No successful treatment is currently available except for acetylcholinesterase inhibitors, which augment cholinergic function, but this is not curative and is only a temporary measure.

A recent study has reported that Nerve growth factor (NGF) prevents neuronal death and improves memory in animal models of aging, excitotoxicity, and amyloid toxicity (Tuszynski, 2002), suggesting that NGF may be used for treating neuronal degeneration and cell death in AD. However, convey of NGF into the brain is not possible via peripheral administration; because of its size and polarity, NGF does not cross the blood-brain barrier. To avoid this difficulty, gene therapy approach could be adopted. By utilizing an ex vivo gene therapy approach (genetically modify cells), NGF can be given directly to the brain and diffuse for a distance of 2-5 mm (Tuszynski et al., 1990).

Ex vivo NGF gene delivery was clinically tried in eight mild-AD patients, implanting autologous fibroblasts genetically modified to express human NGF into the forebrain. After

follow-up of 22 months in six subjects, long-term adverse effects were not found. PET scans showed significant increases in cortical fluorodeoxyglucose after treatment (Tuszynski et al., 2005). Genetically modified stem cells could be used in place of fibroblasts to carry new genes for delivery of NGF to prevent degeneration of basal forebrain cholinergic neurons (Flax et al., 1998; Kim, 2004; Lee et al., 2007, Kang et al., 1993).

A blood stem cell growth factor (granulocyte-colony stimulating factor (G-CSF) is routinely administered to cancer patients whose blood stem cells and white blood cells have been depleted following chemotherapy or radiation. The bone marrow was stimulated by G-CSF to produce more white blood cells needed to fight infection; and is also used to enhance the stem cells circulating in the blood of donors before the cells are harvested for bone marrow transplants. (Pavlović et al., 2009; Lee et al., 2010)

Advanced clinical trials are now investigating the effectiveness of G-CSF to treat stroke, and the compound was safe and well tolerated in early clinical studies of ischemic stroke patients. This growth factor could potentially provide a powerful new therapy for Alzheimer's disease that may actually reverse disease, not just alleviate symptoms like currently available drugs (Ramos & Raj., 2009). The researchers showed that injections under the skin of filgrastim (Neupogen®) - one of three commercially available G-CSF compounds - mobilized blood stem cells in the bone marrow and neural stem cells within the brain and both of these actions led to improved memory and learning behavior in the Alzheimer's mice on the basis of reactive microglia derived from stem cells that are destroying deposits of amyloid plaques in brain tissue. So far, a human growth factor that stimulates blood stem cells to proliferate in the bone marrow reverses memory impairment in mice genetically altered to develop Alzheimer's disease (Ramos & Raj., 2009). The G-CSF significantly reduced levels of the brain-clogging protein beta amyloid deposited in excess in the brains of the Alzheimer's mice increased the production of new neurons and promoted nerve cell connections.

Researchers at the Kyungpook National University in Daegu, South Korea, tested the potential therapeutic effects of bone marrow-derived MSCs in mice. The 2009 study was able to successfully confirm that BM-MSC transplantation accelerated the removal of amyloid- β plaques from the brains of acute AD mice, this study also showed that the BM-MSCs can induce normally-quiescent microglia to clear out amyloid- β build-up (Lee et al., 2009). The three professors who performed the 2009 study in Korea reported in early 2010 that the decreased amyloid- β deposition was directly related to microglial activation (Lee et al., 2010). They also showed that the microglia ameliorate memory deficiencies in the AD mice. This finding was supported by a version of the Morris water maze test known as the hidden platform. Subjects which received PBS injections deteriorated as expected in their ability to learn and memorize the maze, while those treated with BM-MSCs displayed navigational patterns that resembled control subjects. Moreover, they reported that the MB-MSC transplantation was able to reduce tau hyperphosphorylation (Lee et al., 2010).

3.3 Huntington's disease

A neurodegenerative disorder (Huntington's disease (HD) is characterized by involuntary choreiform movements, cognitive impairment, and emotional disturbances (Greenmayre and Shoulson, 1994; Harper, 1996). In spite of identification of the HD gene and associated protein, the mechanisms involved in the pathogenesis of HD remain largely unknown.

A recent research has documented improvements in motor and cognition performance in HD patients following fetal cell transplantation (Bachaud-Le'vi et al., 2000). This research

follows previous reports on experimental HD animals that positive effects of fetal striatal cell transplantation ameliorate neuronal dysfunction (Nakao and Itakura, 2000) and that striatal graft tissue could integrate and survive within the progressively degenerated striatum in a transgenic HD mouse model (Dunnett et al., 1998; Freeman et al., 2000).

A restrictive factor in the transplantation of fetal striatal cells is the difficulty in supplying sufficient amounts of embryonic striatal tissue and the concomitant ethical issues associated with the use of human embryonic tissue. A perfect source of cell transplantation in HD would be NSCs, which could participate in normal CNS development and differentiate into regionally appropriate cell types in response to environmental factors. Prior studies have shown that NSCs isolated from embryonic or adult mammalian CNS can be propagated *in vitro* and subsequently implanted into the brain of animal models of human neurological disorders, including HD (Brustle and McKay, 1996; Flax et al., 1998; Gage, 2000; Temple, 2001; Gottlieb, 2002; Lindvall and Kokaia, 2006).

Genetically modified NSCs producing neurotrophic factors and transplantation of NSCs to replace degenerated neurons have been used to protect striatal neurons against excitotoxic insults (Bjorklund and Lindvall, 2000).

Recently, human NSCs were injected intravenously to counteract neural degeneration in HD model rats and demonstrated functional recovery in grafted animals (Lee et al., 2005, 2006).

3.4 Amyotrophic Lateral Sclerosis

3.4.1 Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by progressive dysfunction and degeneration of motor neurons occur not only in the spinal cord (lower motor neurons) but also in the cerebral cortex and brainstem (upper motor neurons). Muscle weakness progresses rapidly and death occurs within a few years. There are currently no effective treatments for ALS (Wolfson et al,2009).

The expectation for ALS patients is that stem cell transplantation will replace motor neurons, leading to the recovery of neuromuscular functions. Unfortunately, the expectation that stem cells will play such a regenerative role in patients with ALS is unrealistic because of the complexity of the task, a more realistic expectation for stem cells is that they play a supportive role in maintaining the viability of or extending the function of surviving motor neurons (Silani et al,2002).

Inducing stem cells to differentiate into supporting cells, glia, or interneurons that might produce factors that would support motor neurons, or perhaps the stem cells themselves might produce such factors (Svendsen et al,2004) .

3.4.2 Stem cells for treating ALS: current developments

3.4.2.1-Neural stem cells (NSCs) is a challenging therapeutic strategy for treatment of ALS. To provide insight into the potential of the intravenous delivery of NSCs, Mitrečić, and his colleagues, (2010) evaluated the delivery of NSCs marked with green fluorescent protein to the central nervous system (CNS) via intravenous in an ALS model. Highly efficient cell delivery to the CNS was found in symptomatic ALS (up to 13%), moderate in presymptomatic ALS (up to 6%), and was the lowest in wild animals (up to 0.3%). The study provides basic facts about the process occurring after NSCs leave the blood stream and enter the nervous tissue affected by inflammation or degeneration, which should help facilitate the planning of future bench-to-bedside translational projects.

3.4.2.2-Haemopoietic stem cell : Preliminary trials with autologous hematopoietic stem cells have been reported in humans. In one, peripheral blood-purified CD34+ cells were injected intrathecally into 3 patients with ALS (Appel et al,2008, Janson et al 2001)) None reported side effects after 6-12 months, but no clinical efficacy was reported. In another, Deda and collaborators(2009) reported follow-up results one year after stem cell transplantation. The post-operative status of nine patients indicate a significant improvement in comparison to the pre-operative status, as confirmed by electroneuromyography.

3.4.2.3-Mesenchymal bone marrow stem cell: are currently used as an alternative therapy in amyotrophic lateral sclerosis (ALS) patients. Cho, et al 2010 isolated BM-SCs from 11 ALS patients and characterized their potential secretory capacity of neurotrophic factors and they noticed that ALS-SCs have diminished capacity as trophic mediators and may have reduced beneficial effects in cell therapy& suggested that MSCs at early passages are more suitable for stem cell therapy in ALS patients because of their stability and more potent anti-inflammatory and neuroprotective properties (Choi, et al,2010).

Marzzini 2003 ,study the effect intraspinal transplantation of MSCs on 7 patients , Minor postoperative adverse events were transient, but muscle strength continued to decline. Three months later, however, the investigators reported a trend toward slowing of the decline in the proximal muscle groups of the lower limb in 4 patients and a mild increase in strength in 2 patients. The absence of placebo controls and longer follow-up preclude any inferences of efficacy from this study. Karussis and his collauge 2010, prove in phase I trial using intrathecal with or without intravenous MSCs in patients with ALS, Transplantation is clinically feasible and relatively safe procedure with stability of the mean Amyotrophic Lateral Sclerosis Functional Rating Scale [ALSFRS] score.

3.4.2.4- Induced pluripotent stem cell: The generation of pluripotent stem cells from an individual patient would enable the large-scale production of the cell types affected by the patient's disease, using induced pluripotent stem (iPS) cells overcomes the ethical problems of using embryos. (John et al,2008) can make reprogramming of human fibroblasts to induced pluripotent stem (iPS) cells from skin biopsy of an 82-year-old woman diagnosed with a familial form of amyotrophic lateral sclerosis (ALS). These patient-specific iPS cells possess properties of embryonic stem cells, they were successfully directed to differentiate into motor neurons, the cell type destroyed in ALS.

These preliminary hope needs to be tempered with caution because of the early stages of stem cell research in general, and in ALS in particular.

3.5 Spinal Muscular Atrophy

Spinal muscular atrophies (SMA) present a heterogenic group of hereditary neurological diseases and one of the types of motor neuron disease. It is a common "rare disorder", affecting approximately 1 in 6000 babies born, to date no cure exists. The primary approaches to treating or curing SMA have now focused on two strategy options, the first, genetic therapy - manipulating the genetic material responsible for producing SMA. While the second is cellular replacement therapy - replacing dead or dying motor neurons.

Stem cell strategies are presently under investigation, although significant preclinical work and methodological advances remain ahead before these approaches can become clinically relevant (Douglas et al; 2010).

The goal of transplantation is providing a pool of cells that are able to support endogenous neurons through delivery of neuroprotective factors and providing a replacement population for lost motor neurons. In Vitro Stem-cell-derived motor neurons have been

shown to grow axons and successfully form neuromuscular junctions (Gao *et al*;2007, 2005; Wichterle *et al*;2002), and stem cell transplants have lead to growth of axons and some recovery in paralyzed rats (Deshpande *et al*;2006; Harper *et al*; 2004). Induced pluripotent stem cells have been derived from patients with SMA and used to generate motor neurons that show selective deficits compared with wild-type motor neurons in culture (Ebert *et al*;2009).

Spinal-cord-derived neural stem cells have been successfully transplanted into the mouse model of SMA, with a modest improvement of the clinical phenotype and generation of a viable population of motor neurons (Corti *et al*;2008).

A subsequent study using pluripotent stem cells demonstrated similar successful stem cell engraftment and differentiation with improved survival and functional improvement in treated *SMA Model* compared with controls, demonstrating the therapeutic potential of this approach (Corti *et al*; 2010).

Although these reports suggest the possibility of stem cell therapy, several challenges must be addressed before the successful implementation of stem cell therapy can be fully realized. For this strategy to be applicable, large numbers of stem cells need to be generated, to successfully populate the nervous system, properly differentiate into motor neurons and, critically, must successfully and correctly extend axons to and synapse upon muscle targets. It still remains unclear when this therapeutic strategy will become a practical approach in the treatment for SMA in the human population.

3.6 Brain tumor

Despite extensive surgical excision and radiotherapy and chemotherapy; malignant brain tumors such as glioblastoma multiforme remain virtually untreatable and lethal (Black and Loeffler, 1997). The opposition to treatment is associated with their exceptional migratory nature and ability to insinuate themselves seamlessly and extensively into normal brain tissue, often migrating great distances from the primary tumor masses (Dunn and Black, 2003; Sanai *et al.*, 2005). Medulloblastoma is the most common among childhood brain tumors and is incurable. Available treatments including radical surgical resection followed by radiation and chemotherapy have substantially improved the survival rate in this disease; however, it remains incurable in about one-third of patients (Packer *et al.*, 1999). As well, in the case of recurrence, frequently associated with tumor dissemination and the main cause of death, therapeutic options are rarely available (Patrice *et al.*, 1995; Graham *et al.*, 1997).

The capability of human NSCs as an effective delivery system to target and disseminate therapeutic agents to medulloblastomas was demonstrated for the first time (Kim *et al.*, 2006). One of the causes for the recurrence of medulloblastoma in children after standard treatment is the inherent tendency of tumor cells to metastatize through cerebrospinal fluid, leading to leptomeningeal dissemination. Throughout the entire spinal cord, human NSC F3.CD cells were found to distribute diffusely to metastatic medulloblastoma cells after injection in the cisterna magna, and the CD gene in NSCs functioned effectively and killed tumor cells (Shimato *et al.*, 2007).

3.7 Temporal lobe epilepsy

Current studies have shown that transplanted neurons can restore neurogenesis (Kuruba *et al.*, 2009), and GABAergic neurons can reduce seizures (Alvarez-Dolado *et al.*, 2006).

Moreover, one study has shown that a specific type of “stem cell,” transplanted into the dentate gyrus often matures into normal GCs, which could be used in a restorative manner if neurogenesis declines (Carpentino et al., 2008). Remarkably, these stem cells can lead to abnormal growths if a normal animal is used, but in an animal that has had seizures, the stem cells become GCs and tumors do not appear to develop (Carpentino et al., 2008). Infusion of neuropeptide Y may be a particularly effective strategy after such stem cell infusion, because it stimulates precursor division (Howell et al., 2003; Scharfman and Gray, 2006; 2007) and reduces seizures (Noe et al., 2006).

There are four distinct stem cell-based approaches for treating TLE. The first approach involves development of methods for inhibiting increased proliferation of hippocampal NSCs during the first few weeks following the SE. Addressing this issue is important in light of studies suggesting that epileptic seizures such as SE not only increase dentate neurogenesis but also lead to abnormal migration of newly born granule cells into the dentate, where they exhibit spontaneous epileptiform bursts and may contribute to the development of chronic epilepsy (Dashtipour et al., 2001; Parent et al., 2006).

The second approach focuses on developing strategies that activate endogenous NSCs in the chronically epileptic hippocampus to produce a large number of new neurons including GABA-ergic interneurons. This approach has significance because studies in both TLE and animal models of TLE suggest that chronic TLE is associated with dramatically declined production of new neurons in the adult DG. Decreased neurogenesis during chronic epilepsy may contribute to the persistence of seizures possibly due to decreased addition of new GABA-ergic interneurons.

The third strategy comprises rigorous analyses of the efficacy of grafts of NSCs placed into the hippocampus after the onset of chronic epilepsy for suppressing seizures and learning and memory deficits. This is because the initial results of stem cell grafting studies in TLE models reported (Shetty & Hattiangady.,2006, Acharya et al.,2007) are promising in terms of their short term survival and their effectiveness for reducing the frequency of seizures and findings of delivery of anticonvulsant compounds such as NPY, glial-derived neurotrophic factor, and adenosine is efficacious for reducing seizures in animal models of TLE (Noe et al., 2007; Li et al., 2007).

A fourth approach would be a combination therapy comprising NSC cell transplants and cell or recombinant viral vector-based delivery of anticonvulsant compounds into the hippocampus during chronic epilepsy. This plan may be very efficient, as seizure control would likely be mediated by both GABA-ergic interneurons derived from NSC transplants and anti-convulsant compounds released by genetically engineered cells. (Shetty& Hattiangady., 2007)

3.8 Lysosomal storage diseases

Most affected babies by lysosomal storage diseases show a diffuse CNS involvement (Meikle et al., 1999). At present, no effective treatment is available for most of the lysosomal diseases, because the blood-brain barrier bars entry of enzyme preparations into the brain (Sly and Vogler, 2002). However, therapeutic levels of enzymes could be achieved in the brain of animal models of lysosomal diseases by direct inoculation of genetically engineered mouse (Snyder et al., 1995), fibroblasts (Taylor and Wolfe, 1997), or amniotic epithelial cells (Kosuga et al., 2001). In consideration of their widespread migratory ability, normal or genetically modified stem cells would allow widespread delivery of missing enzymes all over the brain. In a mouse model of mucopolysaccharidosis VII (MPS VII), a lysosomal

disease caused by a genetic defect in the activity of b-glucuronidase (b-gluc), genetically engineered mouse overexpressing b-gluc were transplanted into the cerebral ventricle and resulted in reduction of lysosomal storage in the mouse brain (Snyder et al., 1995). Similarly, the transplantation of (b-gluc) overexpressing human NSCs into MPS VII mice and human NSCs migrated extensively all over the brain, produced high levels of b-gluc enzyme, and cleared lysosomal storage in the neuronal cytoplasm (Meng et al., 2003). In an earlier study, immortalized human NSCs were transplanted in a mouse model of Tay-Sachs disease in which abnormal lysosomal storage of GM2 ganglioside is found in the brain, resulting from total absence of hexosaminidase enzyme activity. After transplantation of human NSCs, there was a clearance of storage in neuronal cytoplasm in Tay-Sachs model mice (Flax et al., 1998). The results indicate that NSCs could serve as an excellent gene transfer vehicle for the treatment of diffuse CNS pathology in human lysosomal storage diseases, including Krabbe disease, Gaucher's disease, metachromatic leukodystrophy, and adrenoleucodystrophy.

3.9 Multiple sclerosis

3.9.1 Introduction

MS is a chronic, demyelinating disease of the brain and spinal cord, MS is heterogeneous disease, and so the degree of the disease can range from fairly benign to extremely debilitating and the stages of disease can range from only relapses to progressive (Weiner; 2009)

Unfortunately, the available treatments (Immunomodulatory and immunosuppressive) are not curative, they can reduce CNS inflammation and may delay progression, but control of disease is unsatisfactory in many patients, a logical treatment approach to enhance neuroprotective mechanisms and to induce neuroregeneration through stem cell transplantation, stem cell therapy for MS can be categorized into immune reconstruction or tissue reconstruction (remyelination), two distinct approaches can be considered to promote myelin repair, in one the endogenous myelin repair processes are stimulated through the delivery of growth factors, and in the second the repair process is augmented through the delivery of exogenous cells with myelination potential. Also, the effective treatment of MS requires modulation of the immune system, since demyelination is associated with specific immunological activation (Karussis & Kassir; 2007)

Several types of stem cells having the capacity for promoting myelin repair, as well as modulating the immune response, are potential candidates for MS therapy (Emily et al; 2007).

3.9.2 Stem Cells for treating MS: current developments

3.9.2.1 Embryonic stem cells (ESCs)

When transplanted in rodent models of induced demyelination, embryonic stem cells were shown able to differentiate into glial cells and re-ensheath demyelinated axons in vivo (Brustle et al, 1999; McDonald et al; 1999). Researchers have underlined that ESCs could be a "double-edged sword" since they may cause the formation of a non-homologous implant and teratomas within the organ of transplantation (Brustle et al; 1999, Deacon et al, 1998; Yanai et al; 1995).

3.9.2.2 Adult stem cells

can be detected in both fetuses, and adults. They can be harvested from different tissues: adipose tissue (Gimble & Guilak; 2003), bone-marrow (hematopoietic-HSC (Wognum et

al;2003), mesenchymal-MS (Pittenger,1999 ; Prockop et al;1997), CNS (neural stem cells-NSC, neurospheres) , olfactory bulb (Roisen et al;2001) and others. Several studies suggested the neuroregenerative, the immunomodulatory potential of these adult stem cells (puissant et al;2005 ,Yu et al;2006).

3.9.2.2.1 Adult neural stem cells (NSCs)

In a study by Pluchino et al; 2003 it was shown that adult neural stem cells cultured and injected into EAE-mice – intravenously (iv) or intracerebroventricularly (icv), could migrate into the demyelinating CNS area and differentiate into mature brain cells. It was apparent in this study, that oligodendrocyte progenitors were especially increased, in this model. Clinically, EAE symptoms were strongly down-regulated in the transplanted animals. Despite these promising results, NSC are still not considered the perfect stem cell population for cell replacement therapy and are associated with significant drawbacks. The difficulty is in culturing neurospheres from regions of the adult brain that do not normally undergo self-renewal (Shihabuddin et al;2000) neurosphere-derived cells do not necessarily behave as stem cells when transplanted back into the brain and thus form a focus for immune rejection.

3.9.2.2.2 Hematopoietic stem cells

Autologous Hematopoietic stem cells (HSCT) was largely preferred to allogeneic transplantation because of the lower risk of severe toxicity (van Gelder & van Bekkum; 1995). Briefly, patients with autoimmune diseases can be considered for HSCT if: (i) their disease is severe enough to cause an increased risk of mortality or advanced and irreversible disability; (ii) the disease has been unresponsive to conventional treatments, so, Fassas and his collauege; 2003 recommended practice points to AHSCT for MS patients

(a) AHSCT seems to be the best anti-inflammatory treatment as evidenced in MRI scans. Its clinical value remains to be validated in controlled trials.(b) MS types characterized by neurodegenerative pathogenic components are unlikely to benefit from ASCT.(c) Good candidates are young patients with rapidly evolving RR-MS or “malignant” MS. Also, patients with SP-MS having EDSS scores below 6.5, evidence of inflammation in the CNS, and clinical worsening during the last year.(d)Intense conditioning or extensive T depletion increase the morbidity & mortality risk

3.9.2.2.3 Mesenchymal stem cells (MSCs)

initially isolated from bone marrow but are now shown to reside in almost every type of connective tissue (Da silva et al; 2006). The use of bone marrow derived MSC provides several advantages over conventional neuronal, embryonic and hematopoietic stem cells: (1) they can be obtained from the adult bone marrow; (2) they can be easily cultured and expanded in large numbers; (3) they can be injected autologously without the need of immunosuppressive means to risk for induction of malignancies, as compared to other types of stem cells prevent rejection; and (4) they are less prone to genetic abnormalities during multiple in vitro passages these cells have been shown to have differentiation capacities as well as paracrine effects via the secretion of growth factors, cytokines, anti-fibrotic or angiogenic mediators (Djouad et al ; 2009). A large body of studies also indicates that MSCs possess an immunosuppressive function both *in vitro* and *in vivo* (Karussis & Kassis; 2008). How mesenchymal stem cells affect functional recovery in the damaged adult CNS is not well understood. Fig (3) represent MSC Potential for Therapeutic Applications in autoimmune disorders

They have therefore been tested in the EAE (Ren et al;2009) MSCs were shown to decrease the clinical signs associated with demyelination when injected before or at the onset of the disease, thus demonstrating the therapeutic efficacy of MSCs (Zappia et al;2005). This effect was associated with immune suppression of effector T cells leading to IL-2 reversible T-cell anergy. Subsequently, it was reported that MSCs inhibited T-cell activation with reduced IL-17 and TNF α levels via the secretion of CCL2 by MSCs (Rafie et al;2009) The preclinical studies, (Asano et al; 2006, Draper et al,2004, Lee et al;2001).

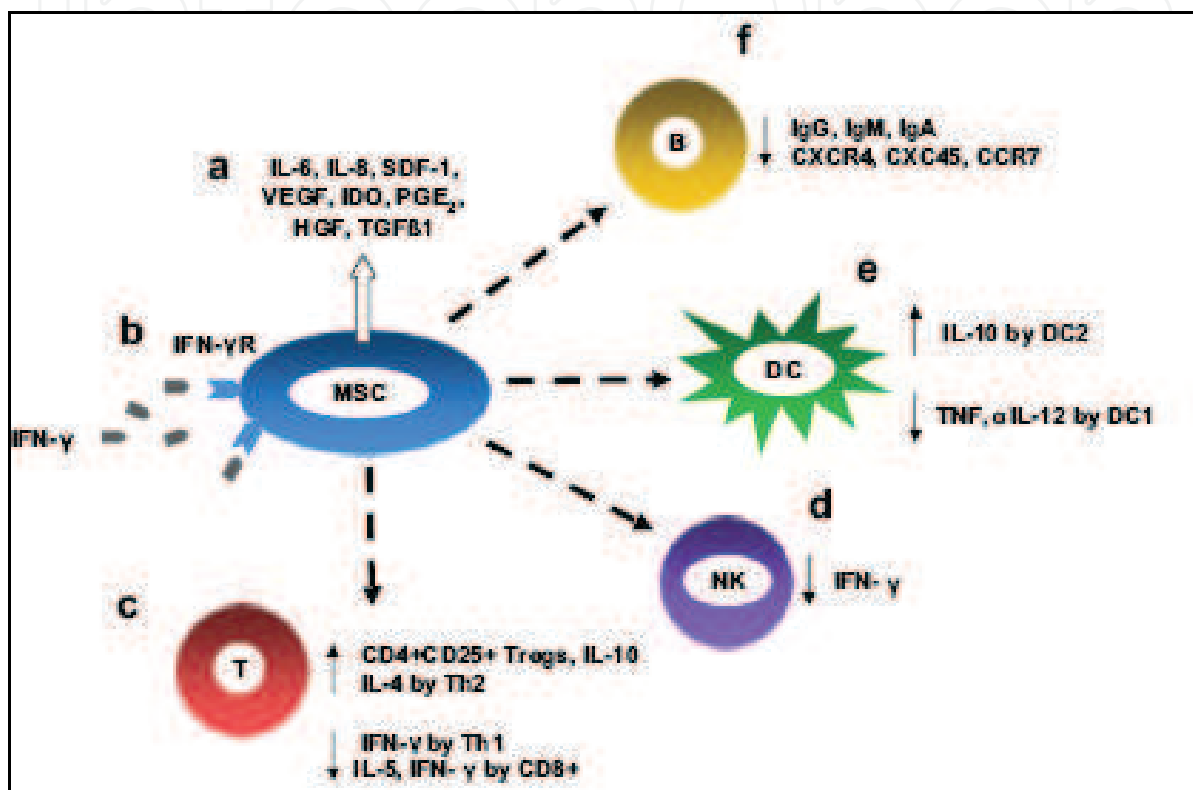


Fig. 3. The immunomodulatory effect of MSCs. (a) A number of soluble factors secreted by MSCs can suppress the activity of inflammatory immune cells. (b) This suppressive activity can be enhanced by the presence of pro-inflammatory cytokines secreted by immune cells such as IFN- γ . (c) The proportion of regulatory T cells and levels of IL-10 production are increased by MSCs. MSCs induce a bias towards a Th2 response and upregulate the production of IL-4. The production of IFN- γ by Th1 cells is reduced. MSCs suppress CD8 T cells prior to activation and reduce production of IL-5 and IFN- γ . (d) MSCs can reduce the production of IFN- γ by NK cells. (e) DC differentiation, maturation and antigen presentation is inhibited by MSCs. The production of pro-inflammatory cytokines is reduced while IL-10 production is upregulated. (f) At high concentrations MSCs inhibit proliferation of B-cells, reduce the levels of IgM, IgG and IgA and downregulate the expression of several cytokine receptors (Payne et al;2008)

Together with the cumulative data from ongoing clinical trials with MSCs in various clinical conditions (reviewed by Giordano et al2007), provided the scientific basis for many (Karussis et al ;2010, Mohyeddin Bonab et al ;2007, Riordan et al;2009). phase 1/2 pilot clinical trial using combined intrathecal and / or intravenous injection of bone marrow- derived autologous MSCs which preliminary prove the feasibility and safety of this type of cell

therapy, in the form of early clinical stabilization or improvement in some of the patients which could be related to these immunomodulating effects and the possibility of neuroprotection and neuroregeneration through transdifferentiation of MSCs into cells of the neuronal or glial lineage, although further controlled trials are warranted to evaluate the long term safety and the potential clinical efficacy of MSC transplantation. The current data indicate that MSCs represent a promising alternative strategy in the treatment of MS however, many questions remain to be addressed, about a better understanding of the underlying mechanisms of immune suppression as well as satisfying safety concerns as regards the *in vivo* survival, formation of ectopic tissue and malignant transformation.

3.10 Stroke

3.10.1 Introduction

Stroke is the third leading cause of death in the USA and can be caused by the occlusion of small vessels in the brain that resulting in subsequent neuronal death. This will trigger a cascade of events including a wide spread inflammatory response. Current therapies for ischemic insults include thrombolysis through treatment with tissue plasminogen activator (tPA). (Bliss et al.; 2010). Stem cell transplantation offers an exciting new therapeutic avenue for stroke not only to prevent damage, which has been the focus of conventional therapeutic strategies, but also to actually repair the injured brain in ischemic (Bliss et al., 2007) and hemorrhagic stroke (Andres et al., 2008).

3.10.2 Therapeutic time window for stem cell therapy in stroke patients

The majority of pre-clinical studies transplanted the stem cells within the first 3 days after stroke and they have mostly used bone marrow- or blood-derived cells (Bliss et al., 2007; Locatelli et al., 2009). This time window is greater than the 3- to 6-h window required for tPA therapy, the only treatment for stroke that currently exists. Cell enhanced recovery has also been reported with sub-acute (1 week post-stroke) and chronic (3 weeks post-stroke) delivery of many cell types including neural cells (Borlongan et al., 1998; Chen et al., 2001a,b; Daadi et al., 2008; Shen et al., 2007; Zhao et al., 2002). Comparison of the results to identify an optimum time for transplantation is difficult as the studies used different models of stroke, cell types, methods of cell delivery, and behavioral tests to assess efficacy. The optimum time for transplantation may be dependent on (a) the cell type used, (b) their mechanism of action. If the treatment strategy is focused on neuroprotective mechanisms, the acute delivery will be critical, however, if the cells transplanted were meant to enhance endogenous repair mechanisms (e.g. plasticity and angiogenesis), then sub-acute delivery would be essential as these events are more prevalent in the first few weeks after ischemia (Carmichael, 2006; Hayashi et al., 2003), (c) route of administration such as intravascular transplantation may require early administration as the cells use inflammatory signals to home to the injured brain (Guzman et al., 2008; Park et al., 2009; Pluchino et al., 2005) and (d) location of infarction, the majority of pre-clinical studies show cell-enhanced recovery after striatal lesions (Bliss et al., 2007; Guzman et al., 2008; Hicks and Jolkkonen, 2009; Locatelli et al., 2009) although cell-induced improvements with cortical lesions are also reported (Hicks et al., 2009; Shyu et al., 2006; Zhao et al., 2002). However, not all studies find that cell therapy is effective (Hicks et al., 2008). As shown in table (1) that the timing of transplantation affected the outcome of these trials is not clear, but they at least demonstrate that delivery of cells at different times is feasible.

3.10.3 Ischemic versus haemorrhagic stroke

Ischemic and hemorrhagic strokes differ in their pathophysiology and mechanism of recovery (Xi et al., 2006). For example, there is no salvageable penumbra with intracerebral hemorrhage (ICH) unlike ischemic stroke (Qureshi et al., 1999), and patients with ICH do not suffer from reperfusion injury with its burst of free radical production (Kleinig and Vink, 2009). Toxic blood breakdown products like thrombin, hemoglobin, and iron additionally contribute to neuronal damage after ICH (Hua et al., 2007; Wang et al., 2002). Therefore, it is plausible that hemorrhagic and ischemic stroke may respond differently to cell therapy and should be tested separately in clinical trials (Andres et al., 2008; Wechsler et al., 2009).

Clinical identifier and clinical phase	Cell type	Estimated enrollment	Time of delivery*	Route of delivery	Country
NCT0047357 Phase I	Autologous bone marrow	10	3h-90 days	Intra-arterial	Brazil
NCT00859014 Phase I	Autologous mononuclear bone marrow	10	24 h-72 h	Intravenous	USA
Nct00525197 Phase I/II	Autologous CD34 + bone marrow	10	7 days	Intra-arterial	UK
NCT00950521 Phase II	Autologous CD34 + peripheral blood	30	6-60 months	Intracerebral	China
NCT00875654 Phase II	Autologous MSCs	30	< 6weeks	Intravenous	France

Clinical identifier from clinical trial gov; time of delivery after stroke onset

Table 1. Current clinical cell transplantation trial for stroke

3.10.4 Route of administration

Many of the studies using systemic delivered cells find significant functional recovery with very few (Guzman et al., 2008; Hicks and Jolkkonen, 2009; Li et al., 2002; Vendrame et al., 2004) or sometimes no cells (Borlongan et al., 2004) entering the brain. Modo et al. (2002) found equal functional recovery when cells were grafted in the ipsi- or contralesional hemispheres, the optimum route of human stem cell delivery has not been determined but will ultimately depend on the timing of delivery, the cell type used, and their mechanism of action. human bone marrow cells (HBMC), human umbilical cord blood cells (HUCBC), peripheral blood progenitor cells, and adipose tissue mesenchymal progenitor cells have all been reported to enhance recovery after stroke with intracerebral or intravascular delivery, and with acute (1 day), subacute (1 week), or chronic (1 month) delivery after stroke (Bliss et al., 2007, Guzman et al., 2008, Hicks & Jolkkonen; 2009, Shen et al., 2007). The only clinical use of intravenous injection of ex vivo-cultured autologous MSCs for the treatment of stroke patients was reported by Bango, et al, 2005. showed improvement in Neurological outcomes as determined by the Barthel index and modified Rankin score, Although this trial described

the success and safety of intravenous injection of ex vivo-cultured autologous MSCs, but only five patients were treated with MSCs and therefore the results should be interpreted with caution. Furthermore, evidence that the intravenously injected MSCs were biologically active is indirect and based on a presumed improved functional recovery (Dekeyser; 2005)

3.10.5 Stem cells types for treating stroke: Current developments

A variety of human cell types have been tested in experimental stroke (Bliss et al., 2007): (1) neural stem/progenitor cells, (2) immortalized cell lines, (3) hematopoietic/endothelial progenitors and stromal cells isolated from bone marrow, umbilical cord blood, peripheral blood, or adipose tissue. To become a useful therapeutic option, cells must show efficacy, have a large expansion capacity in culture to meet the eventual clinical demand. Cell transplantation has shown much promise in experimental models of stroke with a diverse array of cell types which reported to enhance functional recovery after ischemic (Bliss et al., 2007) and hemorrhagic stroke (Andres et al., 2008). Such results led to early Phase I and II clinical trials using a cell line of immature neurons (hNT) derived from a human teratocarcinoma, fetal porcine cells, or autologous mesenchymal stem cells (MSCs). These studies focused on the safety and feasibility of cell transplantation therapy. No cell-related adverse effects were reported with the hNT (Kondziolka et al., 2005, 2000) and MSC transplants (Bang et al., 2005). However, 2 out of the 5 patients receiving the porcine cells developed either seizures or aggravation of motor deficits (Savitz et al., 2005); the value of the cell therapy to these adverse effects is unclear.

3.10.5 Potential mechanisms of transplanted cell-mediated stroke recovery

3.10.5.1 Induction of neurogenesis and synapses formation

Human NPCs form synapses with host circuits (Ishibashi et al., 2004; Daadi et al., 2009a). However, only very few synapses are seen, and recovery occurred too early to be attributable to newly formed neuronal connections (Englund et al., 2002, Song et al., 2002).

3.10.5.2 Neuroprotective mechanism

Through secretion of trophic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), glial cell-derived neurotrophic factor (GDNF), and brain-derived neurotrophic factor (BDNF) that are likely to contribute for recovery (Kurozumi et al., 2005; Llado et al., 2004). Li and Chopp, 2009 suggested that MSCs regulate the levels of cell death through release of trophic factors as well as altering the gap junction coupling between astrocytes, this allows these cells to respond more effectively to control damage

3.10.5.3 Immunomodulation and anti-inflammatory mechanism

Intravenous injection of HUCB or direct injection of human MSCs into the hippocampus after global ischemia lead to down regulate many inflammatory and immune response genes and shifted the balance from a pro- to anti-inflammatory response (Ohtaki et al., 2008).

3.10.5.4 Induction of Angiogenesis

Increased vascularization in the penumbra within a few days after stroke correlates with improved neurological recovery in stroke patients (Krupinski et al., 1993; Senior, 2001) transplanted cell-induced blood vessel formation has been reported with BMSCs, NPCs,

HUCBCs and cells from human peripheral blood (Chen et al., 2003; Horie et al., 2008; Shen et al., 2006; Shyu et al., 2006; Taguchi et al., 2004).

3.10.5.5 Activation of endogenous restorative processes

Induction of host brain plasticity and increase in endogenous brain structural plasticity and motor remapping after ischemia is postulated to underlie the spontaneous recovery seen after stroke (Benowitz and Carmichael, 2010; Carmichael, 2006;2008), and cell transplantation may enhance these process. HUCBCs increased sprouting of nerve fibers from the contralateral to the ischemic hemisphere (Xiao et al., 2005), a similar phenomenon recorded with fetal-derived NPCs (Daadi et al., 2009b, Horie et al., 2009). these restorative process not well understood but may signify a natural repair mechanism of the brain that could be enhanced by transplanted cells. MSC-treated rats demonstrated elevated oligodendrocyte precursors, which increased in concert with enhanced white matter areas (Taguchi et al., 2004, Li et al., 2005, 2006; Shen et al., 2006).and also Xin et al., 2010, suggest that MSCs may also locally increase the levels of tPA in astrocytes around the stroke lesion and that this increases neuroprotection and enhances neurite outgrowth.

The pre-clinical evidence shows great promise for cell transplantation as a therapy for stroke. While we can be cautiously optimistic about the reality of such a therapy, many fundamental questions related to the optimal patient (including age, sex, etiology, anatomic location and size of infarct, and medical history), the most appropriate cell type, cell dose, the timing of surgery, the route and site of delivery, the need for immunosuppression, and mechanism of action remain to be answered.

3.11 Cerebral palsy

3.11.1 Introduction

Cerebral palsy is a group of brain diseases which produce chronic motor disability in children, that affect children from all countries and all ethnic backgrounds. The causes are quite varied and range from damage to the brain during pregnancy, labor or shortly following birth and due to the increased survival of very premature infants, the incidence of cerebral palsy may be increasing. While premature infants and term infants who have suffered neonatal hypoxic-ischaemic (HI) injury represent only a minority of the total cerebral palsy population,(Bartley & Carroll.,2003) Maximum repair and regeneration for cerebral palsy patients as listed by Filip et al. (2004) include:treatment of any infections, chemical toxicities, heavy metal poisoning, Oxygen therapies, Neuroprotective diet and therapies that include antioxidant and endogenous stem cell/stress reduction program that continues to promote repair and regeneration

The similar logistics of stem cell therapy in ischemic stroke also applies for the management of cerebral palsy,however, studies in this population are sparse (Mueller et al., 2005).

3.11.2 Stem cell therapy for cerebral palsy: Current development

3.11.2.1 Human neural stem cells (hNSCs)

hNSCs replaced lost cells in a newborn mouse model of brain damage. Mice received brain parenchymal or intraventricular injections of hNSCs derived from embryonic germ (EG) cells. The stem cells migrated away from the injection site they can survive and disseminate into the lesioned areas, differentiate into neuronal and glial cells and replace lost neurons (Mueller et al ;2005)

3.11.2.2 Human umbilical cord stem cells (hUCSC)

1.5 million CD34+/CD133 human umbilical cord stem cells had been injected subcutaneous in adipose tissue adjacent to the umbilicus. Patient with CP experienced clinically significant improvements in cognitive and motor skill function following this. What is intriguing is that many of these children began demonstrating benefit within the first day or so of receiving the injection. The children who demonstrated improvement were infants and toddlers (Singh and Roy, 2008). Clearly too little time elapsed to attribute these positive changes to hUCSC migration to the brain, engraftment and proliferation, however, these early onset clinically significant improvements become explicable when viewed as the end result of growth factor and neurotrophin activity. The hUCSC deposited in adipose tissue causes adipocytes to synthesize blood brain barrier disruptive TNF-alpha and NGF. This would be consistent with published laboratory and animal studies, and with the rapid improvements seen in the treated children (Singh and Roy, 2008, Payne, 2005). Medical College of Georgia researchers are conducting the first FDA-approved clinical trial to determine whether an infusion of stem cells from umbilical cord blood can improve the quality of life for children with cerebral palsy. The study will include 40 children age 2-12 whose parents have stored cord blood at the Cord Blood Registry in Tucson, Ariz (Medical College of Georgia, 2010)..

3.11.2.3. Mesenchymal Bone Marrow stem cells (MSCs)

Padma, 2005 use an intra-arterial infusion of autologous bone marrow stem cells to patients with static encephalopathy including cerebral palsy, it was found that this procedure was feasible, safe and caused improve in neurological functional outcome Chen et al; 2010, proved that MSC transplanted to animal model of Periventricular white matter injury (PVWMI) in preterm infants may have been neuroprotective and indirectly contributed to brain repair which proved by in vivo MRI demonstrated that labeled cells migrated away from the injection site toward lesioned areas in both hemispheres, confirmed by microscopy postmortem, but double-labeling studies found little evidence of differentiation into neural phenotypes. By expert opinion Carroll and Mays (2011), stem cells may be beneficial in acute injuries of the CNS the biology of stem cells is not well enough understood in chronic injuries or disorders such as cerebral palsy. More work is required at the basic level of stem cell biology, in the development of animal models, and finally in well-conceived clinical trials.

3.12 Spinal cord injury

3.12.1 Introduction

Spinal cord injuries result in long-term functional deficits as a result of the failure of severed adult CNS neurons to regrow long distances, connect to their original targets, and restore circuitry. Several factors are thought to contribute to the lack of regeneration of spinal cord axons. These include a reduction in the intrinsic growth capacity of adult CNS projection neurons, the presence of inhibitory cues derived from damaged CNS myelin, and the formation of a glial scar by local astrocytes in response to inflammatory stimuli (Fitch and Silver;2008). There is no cure, and the most common current treatment – high-dose methylprednisolone – is of questionable value (Lindvall & Kokaia;2006). Multiple approaches will be required to generate functional recovery. This hypothesis has recently received strong support from the use of combinatorial therapies directed at intrinsic and environmental regulators of regeneration Cell-based therapy is currently one of the

promising approaches as many studies have shown improvement in sensory or motor function in the presence of various types of grafted stem cells or ex vivo pre-differentiated stem cells (Kadoya et al., 2009).

3.12.2 Rationales for therapeutic use of stem cells for SCI include (figure 4)

3.12.2.1 Replacement of damaged neurons and glial cells

One possible effect of cell therapy is “replacement,” meaning that the grafted cells integrate into the host tissue and replace damaged or lost cells. Several studies have been performed using in vitro expanded neural stem/progenitor cells, which were then implanted into injured animal model for spinal cord. The cells survived and differentiated into neurons, astrocytes, and oligodendrocytes and had a positive effect on functional outcome (Ogawa et al;2002,Okada et al; 2005) Similarly, MSCs can also differentiate into neuron-like cells and glia which stained for the neural proteins (Azizi;1998, Brazelton ;2000, Prockop ;1997, Woodbury;2000, Okano ;2005 , Mezey; 2000, Hofstetter *et al*;2002)

3.12.2.2 Environmental change in the spinal cord that would encourage regeneration

Create a more favorable environment for limiting damage and promoting regeneration, via immunoregulation (Aggarwal & Pittenger, 2005; Noel et al., 2007), expression of growth factors and cytokines (Song et al., 2004), improved vascularization, providing a permissive growth substrate, and/or suppressing cavity formation (Hofstetter et al., 2002). Enhance remyelination and increase the survival of oligodendrocytes Zhang et al; 2008.

3.12.2.3- cell fusion: The implanted adult stem cells may even fuse with the endogenous stem cells of the spinal cord. Some experiments have shown that MSCs have the ability to fuse with a variety of cells(Alvarez-Dolad;2003 ,Terada et al; 2002). Other studies have shown that cell fusion does not exist or if it does, it is specific to the liver (Newsome et al;2003). This concept should be tested within the framework of spinal cord injury in the future.However,the attendant risks of stem cell therapy for SCI—including tumor formation, or abnormal circuit formation leading to dysfunction—must be weighed against the potential benefits of this approach.

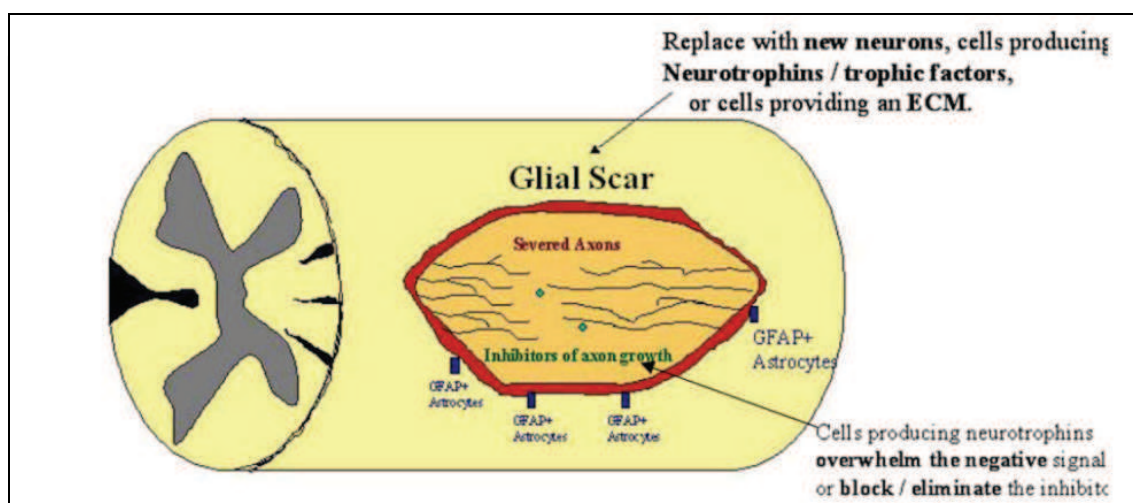


Fig. 4. Possible ways adult stem cells improve recovery in the injured spinal cord (Sherri & Schultz,2005)

3.12.3 Stem cell therapy of SCI: current development

Cell-based therapy is currently a promising approach as many studies have shown improvement in sensory or motor function in the presence of various types of stem cells embryonic stem cells, Blesch et al;2002 olfactory ensheathing glial cells, and Schwann cells (Lima;2006) The bone marrow also contains at least 2 discernable stem cell populations(Jiang et al;2002 , Mazurier et al ;2003)

3.12.3.1.Embryonic stem (ES) cells

Several studies have indicated that rodent ESC-derived neurons can survive, integrate and help restore function following transplantation into spinal cord injured rats (Finley et al., 1996; Lang et al., 2004), Deshpande et al., 2006). Human ESCs have been directed to differentiate into multipotent neural precursors (Carpenter et al., 2001; Reubinoff et al., 2001),and to high purity oligodendrocyte progenitors (Keirstead et al., 2005; Nistor et al., 2005). embryonic and fetal neural stem cells demonstrated stability, sustainability, and expandability in long-term culture systems in order for them to be considered as a possibility in human application. However, serious ethical dilemmas, also lack the ease of accessibility and practicality limit the routine clinical use (Reubinoff et al., 2001).

3.12.3.2 Adult stem cells

Unlike embryonal or fetal origin stem cells, using adult stem cells avoids ethical and moral problems as well as teratogenic and oncogenic risks, a variety of adult stem cells have been implanted in a rat model of spinal cord injury, ranging from olfactory ensheathing cells, and schwann cells (Lima et al;2010) cultured spinal cord stem cells, umbilical cord SC, bone marrow derived stem cells, dermis derived stem cells (Sahn & Kessler;2010)

3.12.3.2.1 Human Neuronal stem cell (NSCs)

NSCs have been preferred in SCI studies because NSCs have the definite ability to differentiate into functional neurons and glial cells after being transplanted in the injured spinal cord (Kim et al; 2007, Johnson et al; 2010. Mothe et al;2008) However, like embryonic stem cells, clinical application of adult NSCs, requires careful preclinical evaluation of their safety , efficacy, purity of the neural cultures as well as there are bioethical issues to be considered (Daar et al;2004, Henon;2003, Riaz et al; 2002)

3.12.3.2.2 Olfactory ensheathing glia cells (OEC's)

“OEC's have been shown to penetrate the inhibitory glial scar at the injury site, and then migrate to their correct targets, restoring function. OEC's could also provide an extracellular matrix and other types of neurotrophins to the injured neurons and neural differentiated adult stem cells, OECs are themselves not considered stem cells(Lima et al;2010). AS they are the patient's own cells, there is no concern regarding rejection (Lima et al;2006).

3.12.3.2.3 Human umbilical cord stem cells (hUCB)

The hUCB cells are immune naïve and so they subsequently cause less graft rejection, GvHD and post-transplant infections (Knutsen & Wall;1999,Newcomb et al ; 2007, Tse & Laughlin; 2005,) and they are able to differentiate into neural lineage. Evidence has emerged suggesting alternative pathways of graft-mediated neural repair that involve neurotrophic effects. These effects are caused by the release of various growth factors that promote cell survival, angiogenesis and anti-inflammation, and this is all a side from a cell replacement mechanism (Park et al ; 2011), Willing and his colleague (2003) prove that, hUCB cells can

be administered by an intraarterial or intravenous route as well as by the direct intralesional approach. Intravenous injection of mononuclear hUCB cells was at least as effective and/or more effective at some points than direct implantation.

3.12.3.2.4 Mesenchymal stem cells (MSCs)

Autologous bone marrow-derived stem cells are ideal candidates for treating SCI in emerging clinical studies, because there are no ethical obstacles to their use and the health risk for patients with SCI is rather small (Park et al; 2005). Numerous electrophysiological and histological preclinical studies have revealed feasibility and beneficial potential of implantation of stem cells from bone marrow in animal models of SCI which showed, neuronal and axonal regeneration, astrocyte proliferation, remyelination, neovascularization, and functional improvement (Akiyama et al;2002a,b, Chopp et al ;2000, Hofstetter et al;2002, Inoue et al;2003, Jendelova et al;2004, Kalyani et al;1998, Saporta et al;2003, Sykova & Jendelova ;2006 &2005, Sykova et al; 2005, Urdzı'kova et al;2006, Wu et al ;2003). These studies have also shown that the optimal therapeutic window for implantation in animal models of SCI is 7–21 days after injury. As regard mode of cell delivery preclinical experiments in rats with SCI demonstrated that intravenously implanted human bone marrow-MSCs labeled in vitro with iron oxide nanoparticles and followed in vivo by magnetic resonance imaging (MRI), migrate, survive, and home only to the lesion site (Jendelova et al;2004, Sykova & Jendelova ;2005). All these data encourage scientists to initiate many nonrandomized phase I/II clinical studies using autologous BM-MSCs, delivered to the patient by many routes (Geffner et al ;2008) either implanted direct intralesional Park and colleagues 2005 or intra-arterially via a. vertebralis (i.e., close to the lesion site) (Sykova et al ;2006) or less invasive which include intravenous, or Intrathecal (Bakshi et al ;2006, Kishk, et al;2010) into patients with subacute (Park et al ;2005, Sykova et al;2006) or chronic SCI (Sykova et al;2006, Kishk, et al;2010) at the cervical or thoracic level, the outcome from BM-MSC implantation in acute and chronic patients is promising. However, the therapeutic window will play an important role in any type of SCI treatment. There seems to be a similar therapeutic window in humans as in animals, which is up to 3–4 weeks after SCI. Sykova and his colleague ;2006 suggest that administering the cells closer to the injury site, such as through the catheterization of a. vertebralis, or into the cerebrospinal fluid (Kishk et al; 2010, Ohata et al; 2004), or even intraspinally at the lesion border (Park et al; 2005), might be important for a better outcome. The observed partial recovery might be attributable to a “rescue effect,” a reduction in tissue loss from secondary injury processes, as well as to diminished glial scarring. MSCs may induce an allodynia-like response by producing intrathecal proinflammatory cytokines, especially interleukin-1, tumor necrosis factor, and interleukin-6 (Chae et al; 2009). Neither Abrams et al;2009, Sykova et al;2006 or Geffner et al; 2008 reported central pain as a complication. The deployment of MSCs in patients with subacute or chronic traumatic SCI will need longer follow-up, more studies that explore the best timing post injury, the dose and duration of MSC interventions, Objective assessment of the bladder and bowel function with urodynamic studies and anal sphincter EMG is necessary. Imaging of the lesions by MRI using particle-labeled MSCs could determine whether the cells reach the lesion. Future in vivo markers for neuronal regeneration or remyelination could give more insight into the mechanisms of any biological effects (Dobkin 2010)

Clinical studies are necessary, However, the question of which cell type is most beneficial for SCI treatment is still unresolved as what are the mechanisms underlying the beneficial

effect(s) The therapeutic window, the implantation strategy, the method of administration, the number of cells, and the possible side effects can only be tested in human clinical trials guided by Guidelines for trials of cellular therapies (Fawcett et al;2007) .

4. Conclusion

It is realistic to believe that stem cells will be used clinically, not as a cure-all but as part of a therapeutic armamentarium. The key, however, will be in applying the right cell type to the right disease and conveying the right amount of expectation to the patient. Meticulous attention to the ethics and Collaboration between basic scientists, clinicians, industry partners, and funding bodies is required to translate the potential of cell therapy into a reality in a timely, but safe and effective manner .

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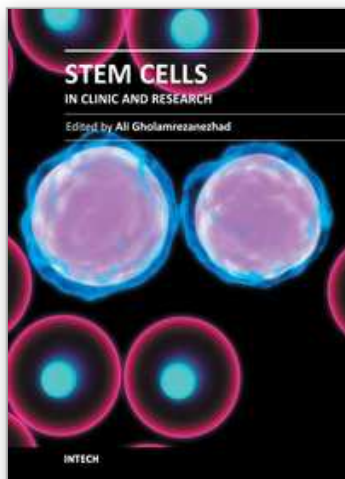
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Based on our current understanding of cell biology and strong supporting evidence from previous experiences, different types of human stem cell populations are capable of undergoing differentiation or trans-differentiation into functionally and biologically active cells for use in therapeutic purposes. So far, progress regarding the use of both in vitro and in vivo regenerative medicine models already offers hope for the application of different types of stem cells as a powerful new therapeutic option to treat different diseases that were previously considered to be untreatable. Remarkable achievements in cell biology resulting in the isolation and characterization of various stem cells and progenitor cells has increased the expectation for the development of a new approach to the treatment of genetic and developmental human diseases. Due to the fact that currently stem cells and umbilical cord banks are so strictly defined and available, it seems that this mission is investigational more practical than in the past. On the other hand, studies performed on stem cells, targeting their conversion into functionally mature tissue, are not necessarily seeking to result in the clinical application of the differentiated cells; In fact, still one of the important goals of these studies is to get acquainted with the natural process of development of mature cells from their immature progenitors during the embryonic period onwards, which can produce valuable results as knowledge of the developmental processes during embryogenesis. For example, the cellular and molecular mechanisms leading to mature and adult cells developmental abnormalities are relatively unknown. This lack of understanding stems from the lack of a good model system to study cell development and differentiation. Hence, the knowledge reached through these studies can prove to be a breakthrough in preventing developmental disorders. Meanwhile, many researchers conduct these studies to understand the molecular and cellular basis of cancer development. The fact that cancer is one of the leading causes of death throughout the world, highlights the importance of these researches in the fields of biology and medicine.

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