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Mesenchymal Stem Cells in CNS Regeneration

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1. Introduction

1.1 Mesenchymal stem cells as an ideal source of cells for regenerative medicine

During the last two decades, stem cells have become recognized as a promising tool for various biomedical applications including disease modeling, drug development, and cell replacement therapies. However, identification of the reliable sources of stem cells that can be easily harvested, expanded on a large enough scale, and carry no risk of immune rejection still remains one of the important issues for regenerative medicine.

Mesenchymal stem cells (MSCs) are promising tools for cell therapy (Zeidan-Chulia & Noda, 2009) by autologous and allogeneic transplantation for two significant reasons. Firstly, MSC can easily be isolated and expanded from different adult and postnatal tissues, such as BM (Prockop, 1997), peripheral blood (Kuznetsov et al., 2001), muscle (J. Y. Lee et al., 2000), vasculature (Brighton et al., 1992), skin (Mizuno & Glowacki, 1996), adipose tissue (Zuk et al., 2001) and umbilical cord (O. K. Lee et al., 2004). Secondly, MSCs can differentiate into multiple cell types of mesodermal, endodermal, and epidermal origin such as bone (Pereira et al., 1995), cartilage (Pereira et al., 1998), fat (Umezawa et al., 1991), muscle (Ferrari et al., 1998), cardiomyocytes (Makino et al., 1999), and neurons (Kohyama et al., 2001). Such a surprising high plasticity of MSCs might be explained by the expression of a variety of gene families in undifferentiated MSCs. Several recent studies have shown that MSCs express several embryonic stem cell markers (pluripotent markers) such as Oct4, Nanog, alkaline phosphatase and SSEA-4, and SOX2 (Park & Patel, 2010; Pierantozzi et al., 2011; Riekstina et al., 2009). It also has been demonstrated that the translational and transcriptional machinery in MSCs responsible for the expression of multiple genes typical of several derivatives of three germ layers are not silenced, rather operating at the low level (Blondheim et al., 2006; Tondreau et al., 2008). Most importantly, at appropriate environmental conditions in vitro and in vivo MSCs can upregulate the expression of these genes and exhibit several characteristics of mature cells of different tissues such as heart (Choi, Kurtz, & Stamm, 2011; Hattan et al., 2005; Makino et al., 1999), lever (Stock et al., 2010) and central nervous system (Alexanian, 2010). While it still many controversy concerning transdifferentiation of MSCs these recent data suggest that MSCs could be ideal autologous source of easily reprogrammable cells. Harboring such a high plasticity these cells, in contrast to adult and other tissue specific stem cells and progenitors, could be manipulated more easily (Niibe et al., 2011).

With the promise that MSCs present for the development of new cell therapies, researchers have pursued a broad range of investigations for their therapeutic utilization (Parekkadan & Milwid; Picinich, Mishra, Glod, & Banerjee, 2007; Stappenbeck & Miyoshi, 2009; Wang, Liao, & Tan, 2011). During the last two decades an overwhelming amount of basic and preclinical research has been accumulated that demonstrates the therapeutic usefulness of MSCs in the treatment of several diseases and injuries such as neurodegenerative diseases (Joyce et al.), spinal cord and brain injuries (Y. Jiang et al.), cardiovascular diseases (Trivedi, Tray, Nguyen, Nigam, & Gallicano), diabetes mellitus (Y. H. Zhang et al., 2009) and diseases of the skeleton (Chanda, Kumar, & Ponnazhagan). In most of these studies, treatment with MSCs results in substantial functional benefit and these pre-clinical studies have led to the initiation of a number of clinical trials worldwide.

MSCs have been used in clinical trials since 1995 and, currently, more than 180 trials are registered with ClinicalTrials.gov for the treatment of several diseases including numerous neurological disorders and injuries such amyotrophic lateral sclerosis, stroke, parkinson's disease, Alzheimer's disease, brain and spinal cord injuries.

2. In vitro neural differentiation potential of MSCs

Demonstration of neural differentiation potential of MSCs in several in vitro and in vivo studies suggests the potential usefulness of MSCs in the treatment of various CNS disorders. This potential has led to extensive studies to further explore the neural plasticity of these cells (Azizi, Stokes, Augelli, DiGirolamo, & Prockop, 1998; Kopen, Prockop, & Phinney, 1999; Munoz-Elias, Marcus, Coyne, Woodbury, & Black, 2004).

During the last several years, numerous in vitro neural induction protocols to produce neural cells from MSCs have been reported. In most induction experiments, MSCs were simply exposed to growth factors, neurotrophic factors or factors favoring neural cell differentiation (Bi et al., 2010; M. Chen et al., 2000; Q. Chen et al., 2005; Joannides et al., 2003; B. J. Kim, Seo, Bubien, & Oh, 2002; S. S. Kim et al., 2005; Kondo, Johnson, Yoder, Romand, & Hashino, 2005; Lim et al., 2008; Long, Olszewski, Huang, & Kletzel, 2005; Padovan et al., 2003; Sanchez-Ramos et al., 2000; Zeng et al., 2011). Other studies have used different culture media, supplemented with individual or various combinations of chemical and pharmacological agents, such as DMSO, b-mercaptoethanol, 5-bromo-2-deoxyuridine (BrdU), butylated hydroxyanisole, forskolin, and dibutyryl cyclic AMP (Ankeny, McTigue, & Jakeman, 2004; W. Deng, Obrocka, Fischer, & Prockop, 2001; Episkopou, 2005; Hermann et al., 2006; Jori et al., 2005; S. S. Kim et al., 2005; Lu, Blesch, & Tuszynski, 2004; Munoz-Elias, Woodbury, & Black, 2003; Tio, Tan, Lee, Wang, & Udolph, 2010; Yang, Wu, & Xiao, 2005; L. Zhang, Seitz, Abramczyk, Liu, & Chan, 2011). Other methods to induce MSCs into cells with neural characteristics include: transfection of MSCs with Noggin and Notch transcription factors (Dezawa et al., 2004; Kohyama et al., 2001); manipulation with surface proteins of culture substrate (Qian & Saltzman, 2004); co-culturing MSCs with NSCs or neural cells (Alexanian, 2005; Chu, Yu, Zhang, & Yu, 2008; Krampera et al., 2007; Wislet-Gendebien et al., 2005; Y. Q. Zhang et al., 2010); and growing MSCs as spheres in cultures (Shiota et al., 2007), transfection of MSCs with microRNA-9 (Jing et al., 2011). In several other studies, MSCs were turned into multipotent stage and then induced into neural cell lineages, by exposing them to appropriate neural differentiation conditions (Alexanian, 2007; Kohyama et al., 2001; Qu et al., 2004). Recently, we proposed an original method for efficient

generation of neural cells from feline and human BM-derived MSCs (hMSC) (Alexanian, 2010; Z. Zhang, Maiman, Kurpad, Crowe, & Alexanian, 2011). In these studies, neural induction was achieved by exposing cells simultaneously to inhibitors of DNA methylation and histone deacetylation and pharmacological agents that increased cAMP levels. The main idea of this methodological approach was the reactivation of pluripotency-associated genes in MSCs simultaneously exposing them to neural-inducing factors. Neurally modified MSCs by this methodology, in contrast to naïve MSCs, express several neural progenitor and mature neural markers demonstrated by real time RT-PCR, western blot, ELISA and immunocytochemistry Fig.1. and Fig.2.

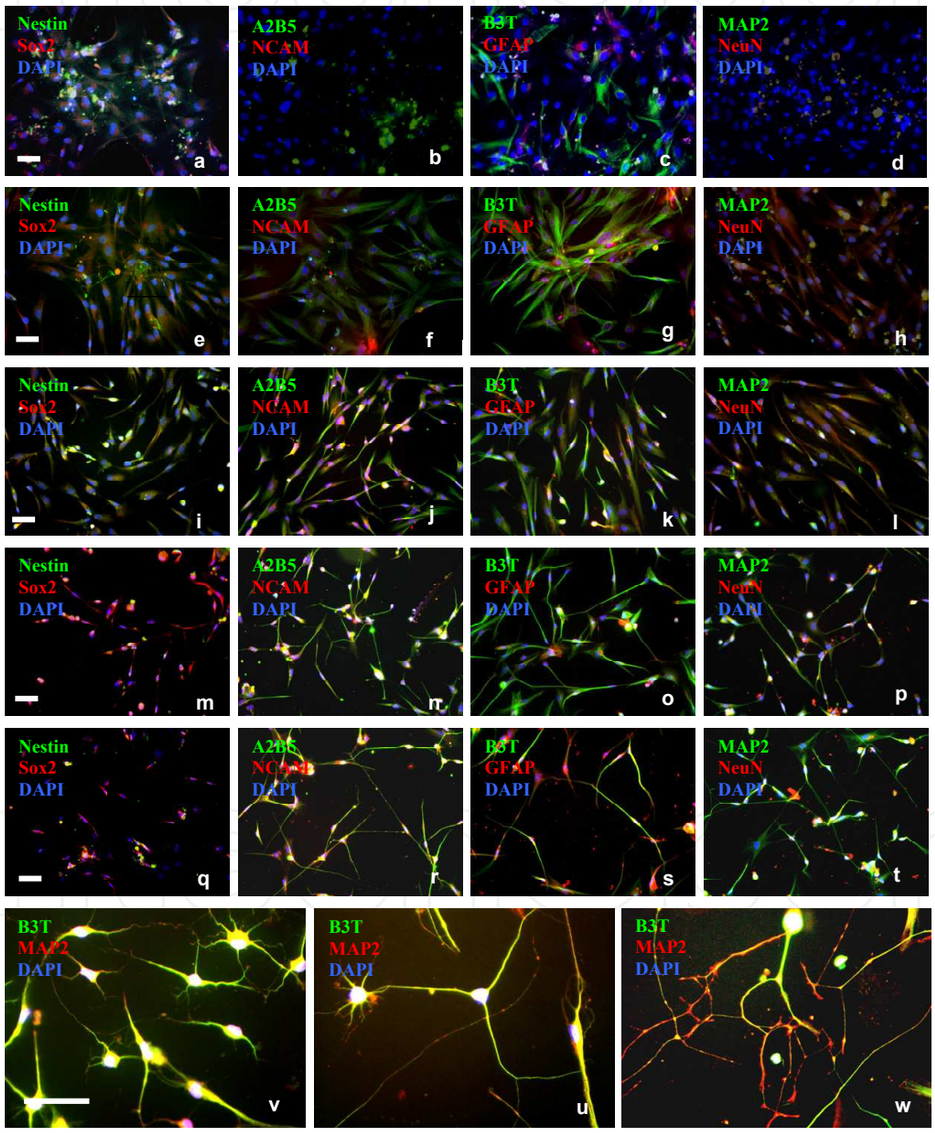

Fig. 1. Expression of neural markers nestin, Sox2, A2B5, NCAM, B3T, GFAP, MAP-2, and NeuN in hMSCs (a-d) and NI-hMSC grown 24h, 1, 2, 3 weeks in neural induction medium (e-t). NI-hMSCs grown an additional week in neuronal induction medium were generated cells with long axon- and dendrite-like extensions (v-w). Bars 40um.

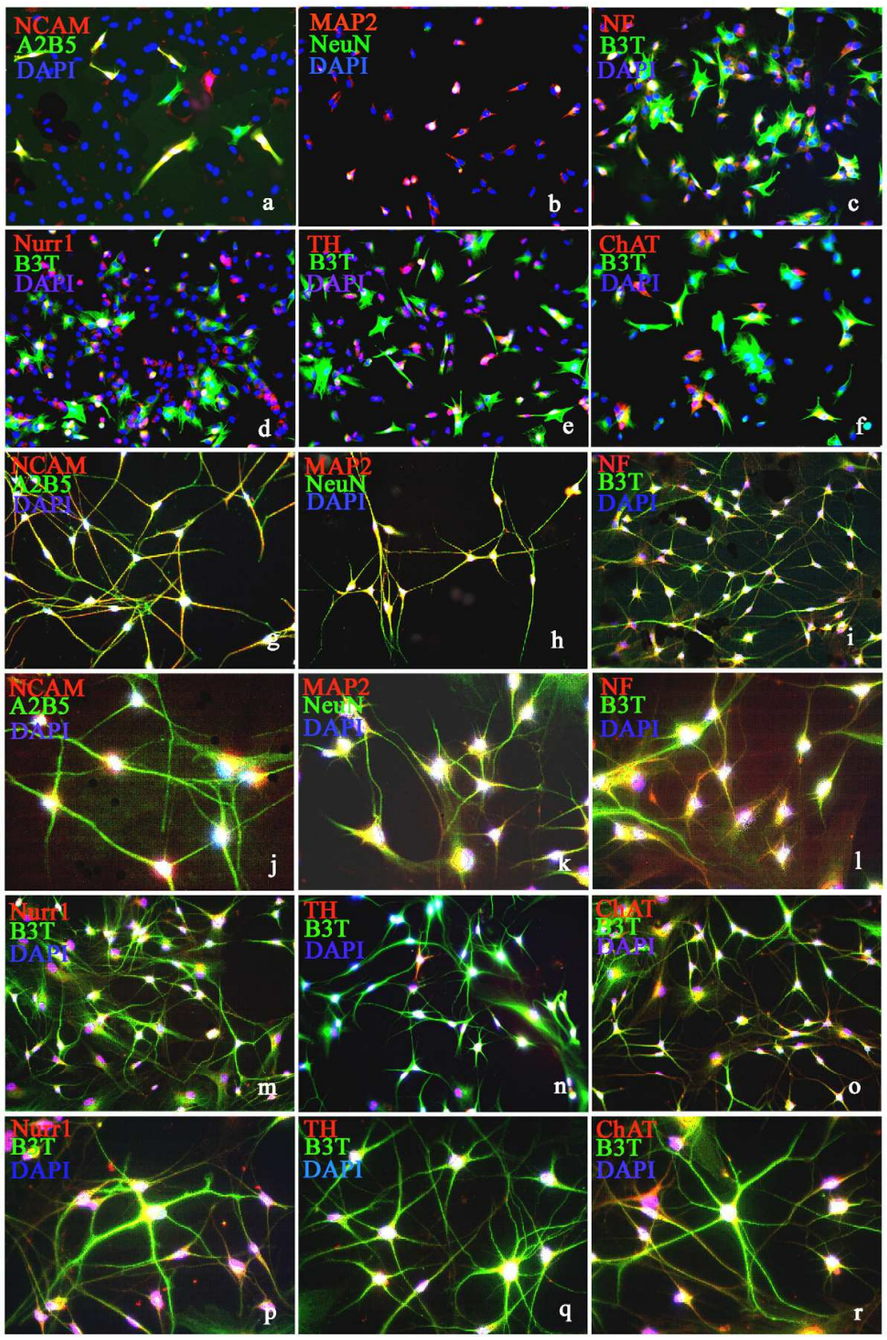

Fig. 2. Morphological and immunocytochemical characterization of unmodified and NI-fMSCs. Expression of neural markers B3T, NCAM, A2B5, MAP2, NeuN, NF, Nurr1, TH and ChAT in unmodified fMSCs (a-f) and in NI-fMSCs grown for 72h in neural induction medium (g-r).

Despite these studies, there is an intense ongoing debate about the nature of these differentiation responses. For example, some recent reports suggested that cell fusion could account for transdifferentiation (Terada et al., 2002). However, spontaneous cell fusion is a

very rare event and, therefore, can not be account for massive transdifferentiation demonstrated in numerous recent studies. In addition, MSCs can be induced into neural-like cells with several neural inducing factors, without being grown in co-cultures with NSCs.

A few other reports suggested that some of these investigations suffered from artifacts created by in vitro chemical stress (Lu et al., 2004; Neuhuber et al., 2004). Nevertheless, Tondreau and colleagues have recently found significant upregulation of neural genes and downregulation of chondrogenic, osteogenic, adipogenic and myogenic genes in neurally differentiated MSCs as demonstrated by microarray analysis (Tondreau et al., 2008). In addition, a numerous studies suggest that with appropriate neural induction protocols, MSCs could produce mature neuron-like cells that exhibit multiple neuronal properties and traits, such as action potential, synaptic transmission, secretion of neurotrophic factors and dopamine, and demonstration of spontaneous post-synaptic current (Alexanian, Maiman, Kurpad, & Gennarelli, 2008; Bonilla et al., 2005; Greco, Zhou, Ye, & Rameshwar, 2008; Hermann et al., 2004; Y. Jiang et al., 2003; S. S. Kim et al., 2008; Mareschi et al., 2009; Trzaska et al., 2009; Wislet-Gendebien et al., 2005). Whether these neurally modified MSCs can produce fully functional neural cells in vitro and vivo is still under intensive investigations.

3. In vivo neural differentiation potential of MSCs

One of the first discoveries that demonstrate the pluripotent nature of adult MSCs in vivo, came from Ferrari et al. who clearly showed that adult murine BM contained cells capable of differentiation into skeletal muscle (Ferrari et al., 1998). In the past decade or more, several other studies have documented the ability of adult BM-derived cells to differentiate into liver and epithelium (Petersen et al., 1999; Theise, Badve, et al., 2000; Theise, Nimmakayalu, et al., 2000), endothelium (Kawamoto et al., 2001; Kawamoto et al., 2003; Takahashi et al., 1999), heart (Kucia et al., 2004; Orlic et al., 2001; Tomita et al., 1999), and brain (Brazelton, Rossi, Keshet, & Blau, 2000; Eglitis & Mezey, 1997; Mezey, Chandross, Harta, Maki, & McKercher, 2000). These striking observations indicate that there are BM cells that can migrate to distant sites and participate in repair of tissues across germ layer boundaries. In the most striking examples, BM cells injected in to the blastocyst contributed to most somatic cell lineages, including neural (Y. Jiang et al., 2002). These discoveries have led to extensive studies to further explore the neural differentiation potential of MSCs in intact, injured and diseased CNS.

However, multiple studies conducted during the last decade showed that MSCs transplanted into the intact, injured or diseased CNS environments do not differentiate or only a small portion of cells produce neural phenotypes (Alexanian, Kwok, Pravdic, Maiman, & Fehlings, 2010; Castro et al., 2002; J. Deng, Petersen, Steindler, Jorgensen, & Laywell, 2006). In contrast, MSCs transplanted in developing embryonic brain or in neurogenic areas of the adult brain expressed heterogeneous traits characteristic of radial glia, subventricular zone progenitors, migratory cells, parenchymal neurons, and glia (Azizi et al., 1998; Kopen et al., 1999; J. M. Li et al., 2011; Munoz-Elias et al., 2004). The fate of MSCs consequently appeared to be regulated by multiple influences, presumably including different microenvironments. These are in close analogy with studies in which pluripotent or highly immature NSCs were used. In a similar way, transplanted cells generated different neural phenotypes when transplanted into one of the few neurogenic areas of the brain [35,36] but remained undifferentiated or differentiated predominantly into the glial cells

when transplanted into injured or non-neurogenic areas [37]. However, when late-stage precursors and immature neurons were transplanted into non-neurogenic or injured brain and spinal cord, more neural differentiation was observed [38,39]. This indicates that, while microenvironment can play a decisive role in determining the fate of engrafted MSCs or NSCs, the intrinsic state of these transplanted cells is another important factor for the commitment of cells to a particular phenotype. MSCs which presumably committed to mesodermal lineages most probably will not produce neural cells in intact, injured or diseased CNS and therefore, manipulation of cells into neural fate maybe required before transplantation. In fact, several recent studies showed that neurally modified MSCs transplanted into intact or damaged CNS exhibited higher ability to generate cells positive to various neural markers (Alexanian et al., 2008; Alexanian, Michael, Zhang, & Maiman, 2011; Cho et al., 2009).

4. Therapeutic effects of naïve and neurally modified MSCs in CNS disorders and their underlying mechanisms

Experimental treatments of CNS disorders can be broadly grouped into the two distinct but interrelated strategies of neuroprotection and neurorepair/neuroregeneration. Neuroprotection refers to inhibition of the death of CNS parenchymal cells in traumantic and neurodegenerative CNS, neurorepair/neuroregeneration refers to the replacement of lost neural cells, stimulation of endogenous neural progenitors and/or regeneration of severed axons or sprouting of intact axons to innervate denervated targets in injured or diseased CNS. MSCs have been used for all of these strategies and exhibited beneficial therapeutic effect in several animal models of CNS injury and neurodegenerative diseases.

4.1 MSC in CNS injury (traumatic spinal cord and brain injury, ischemia/stroke)

Recent multiple studies demonstrated that naïve or neurally modified MSCs derived from different tissue sources exerted therapeutic effect in several animal models of spinal cord injury (SCI). However, the precise mechanisms by which transplantation of MSCs promote functional recovery after SCI is still unclear. A number of mechanisms have been suggested, including the promotion of axon regeneration, neuroprotection, modulation of the immune responses, and trans-differentiation into neural cell types (Chamberlain, Fox, Ashton, & Middleton, 2007; Dezawa, 2002; Enzmann, Benton, Talbott, Cao, & Whittemore, 2006; Keilhoff, Goihl, Stang, Wolf, & Fansa, 2006). The immunosuppressive properties of MSCs (Bartholomew et al., 2002a; Corcione et al., 2006; Di Nicola et al., 2002; X. X. Jiang et al., 2005) may combine to reduce the acute inflammatory response to SCI and hence reduce cavity formation as well as decrease astrocyte and microglia/macrophage reactivity (Abrams et al., 2009; Himes et al., 2006; Neuhuber, Timothy Himes, Shumsky, Gallo, & Fischer, 2005) in injured spinal cords. The therapeutic effect of MSCs on axonal growth could be exerted by creation of a favorable environments such as cellular bridges, guiding strands and scaffolds, secretion of trophic factors, cytokines and production of extracellular matrix (Fuhrmann et al., 2010; Gu et al., 2010; Hofstetter et al., 2002; Neuhuber et al., 2004). The neuroprotective mechanism of MSCs could be multifactorial, such as modulation of immune response and provision of trophic factors (Uccelli, Benvenuto, Laroni, & Giunti, 2011). Whether MSCs therapeutic effect can be exerted via cell replacement is still one of the most debated issues.

In most reported studies, transplanted MSCs either do not differentiate, or only very small percentage of cells survive and produce neural cells in vivo. This led to studies to elucidate whether neural modification of MSCs will promote cell survival and neural differentiation of transplanted cells in intact and injured CNS.

Several recent studies suggest that neural modification of MSC prior to their transplantation can exhibit even higher beneficial therapeutic effect then naïve MSCs. In one of these studies Sung-Rae Cho et al. showed that transplantation of neurally differentiated MSCs derived from bone marrow promoted functional recovery in spinal cord injured rats and the latency of somatosensory evoked potentials were significantly improved compared with those of naïve MSCs and PBS controls (Cho et al., 2009). Furthermore, transplanted cells prelabeled with BrdU also differentiated into neural lineage cells that expressed specific markers for astrocytes and oligodendrocytes 4 weeks after transplantation, even though the number of integrated cells was not abundant. However, these differentiated cells did not survive longer than 8 weeks post transplantation, which was similar to what was reported in a previous studies (4). Because injured rats showed significant motor recovery at a relatively early stage after transplantation, and only a small number of transplanted cells survived in the injured spinal cord for a limited period, authors concluded that trophic or paracrine support could be the main factors for functional improvement.

Recently, we also demonstrated that transplanted neurally induced hMSCs (NI-hMSCs) promoted tissue preservation and improved locomotor recovery of injured animals (Alexanian et al., 2011). Motor recovery that consisted of hindlimb weight support and consistent hindlimb stepping was significantly different at 2-12 weeks post-recovery in the group that was transplanted with NI-hMSCs when compared with the control groups that received hMSCs and PBS (Fig.3).

Histological studies of spinal cord sections at specified distances rostral and caudal to the epicenter demonstrated that at the epicentre and 1mm caudal and rostral from it the percentage of the eriochrome cyanine-positive spared white matter was significantly larger in NI-hMSCs treated group than that in the PBS group (Fig.4.A,B). While there was no significant difference between naïve hMSCs and PBS groups, there was a modest trend for increased white matter sparing in hMSCs-treated versus PBS-treated spinal cords (Fig.4.B).

Stereological assessments of injured spinal cord tissues demonstrated a modest reduction in the percentage of cystic cavities in the NI-hMSCs and hMSCs treated groups versus PBS group (Fig.4.C) (Fig.5). Although no statistically significant difference had been noticed between groups (Fig.4.C), the difference found between NI-HMSCs and PBS was very close to the significance level adopted in the study ($p<0.05$).

Immunohistochemistry data showed that NI-hMSCs were survived at post transplantation weeks 1-12. Analysis of the spinal cord slices of two weeks treated animals revealed that 85% percent of survived cells were positive to B3T (Fig.6.a,b,c,d). A small percentage of cells (2%) was positive to GFAP (Fig.4.e) and 5% to Sox2 (Fig.6.f). By 12 weeks the number of surviving cells declined to 15-20% of that at week 2 and only 10% of survived cells were positive to B3T (Fig.6.g,h,i).

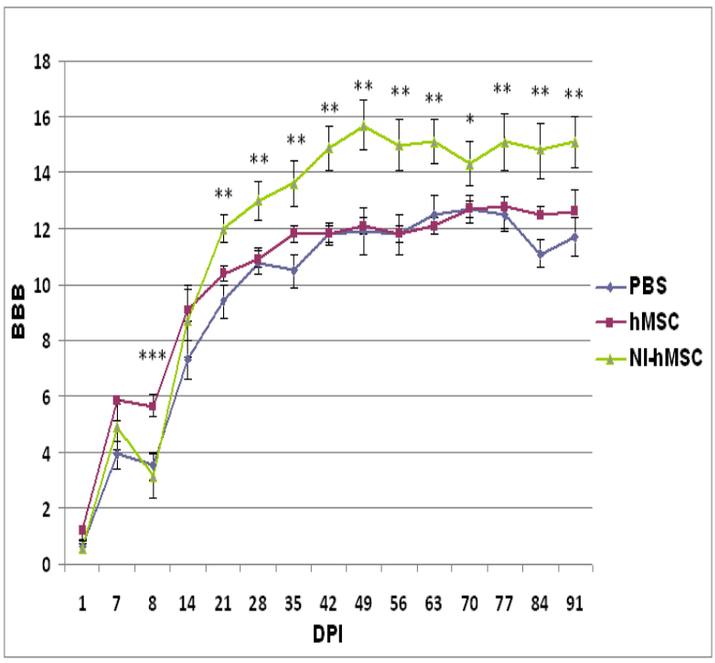

Fig. 3. Locomotor recovery (BBB) scores for the post spinal cord injury (DPI-days post injury) behavioral analysis. The asterisks (*) and (**) indicates a significant differences between the NI-hMSCs transplanted group compaired to the PBS and PBS+HMSCs groups respectively. Asterisk (***) indicates a significant differences between the hMSCs transplanted group compaired to the PBS.

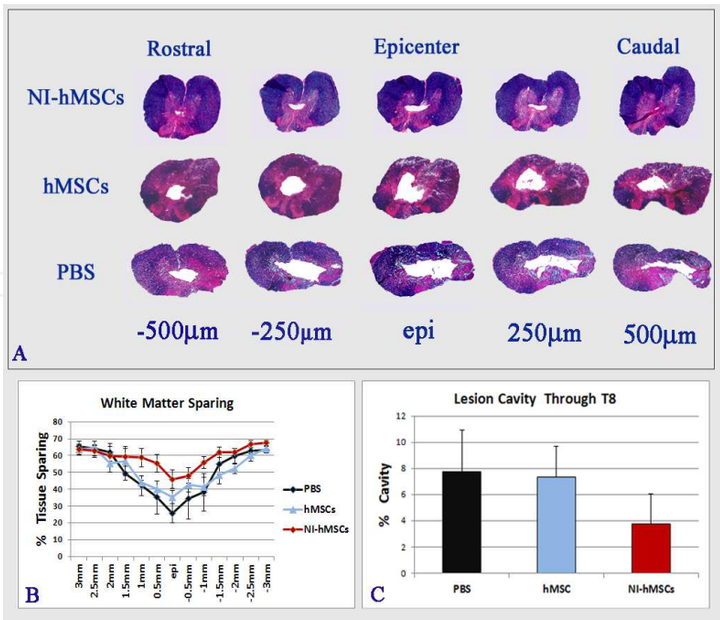

Fig. 4. Analysis of white matter sparing and lesion cavity volumes in NI-hMSCs, hMSCs, and PBS treated groups. (A) Representative spinal cord cross-sections extending 500um rostral and caudal from the lesion epicenter. (B) Graph representing the percentages of

spared white matter through the entire T8 spinal cord segment. (C) Graph representing comparison of the volumes of lesion cavities.

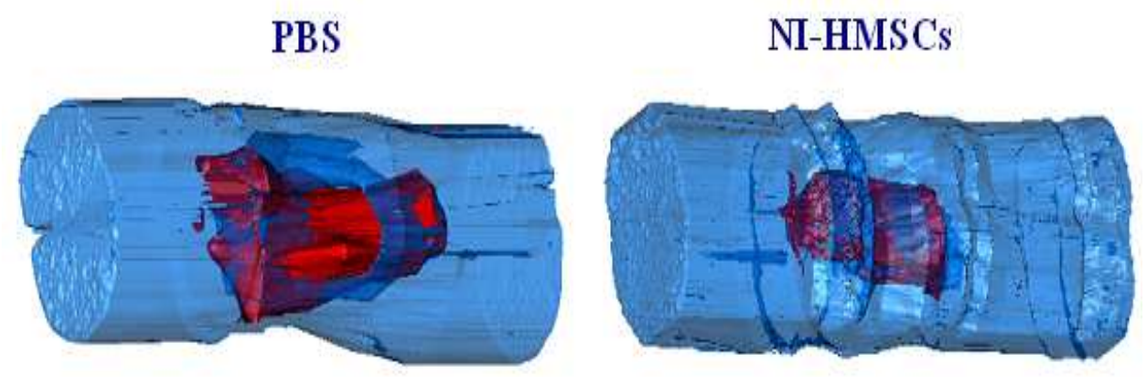

Fig. 5. Representative three-dimensionally reconstructed images of the lesion cavities through T8 injured spinal cord segments of NI-hMSCs and PBS treated animals.

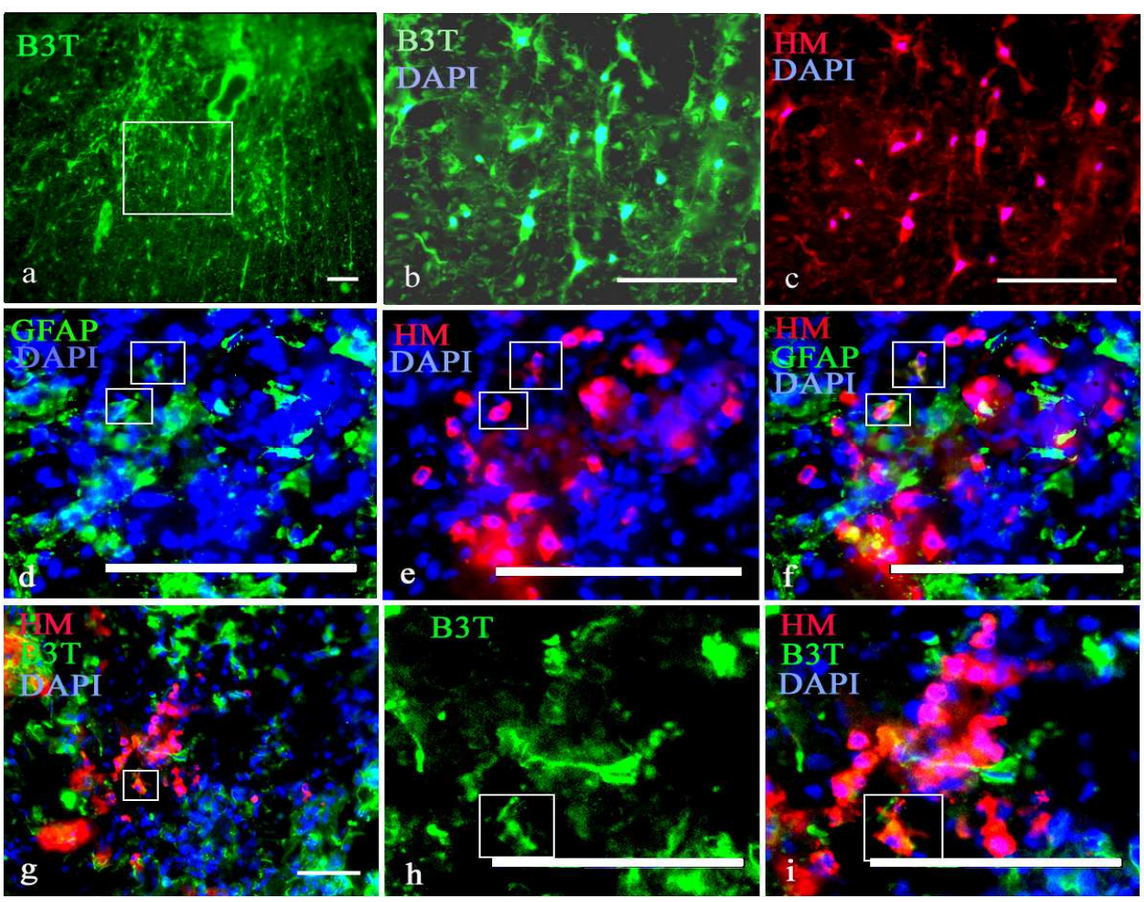

Fig. 6. Transplanted NI-hMSCs survived 2 weeks after transplantation and expressed neural markers such as B3T (a-c, b and c are the higher magnifications of the marked area in the image a), and GFAP (d-f). By 12 weeks the number of surviving cells declined to 15-20% of

that at week 2 and only 10% of survived cells were positive to B3T (g,h,i). The images h and i are higher magnifications of g. HM stands for human anti-mitochondrial antibody.

Thus, MSCs, either neurally modified or not, may provide an alternative source of autologous adult stem cells that could be useful for replacing damaged neural cells in injured spinal cord and/or providing support to spinal cord tissue cells.

Over the last decade or so, MSCs have been also used in experimental repair of the injured brain. Chopp and Li initially demonstrated transplanted MSCs promote functional recovery in rats with traumatic brain injury and attributed the beneficial effects of MSCs to the enhancement of endogenous restorative and regenerative processes (Chopp & Li, 2002). Later, Chopp and his group showed that MSCs treated with neurotrophins NGF and BDNF in vitro led to a higher number of engrafted cells after transplantation into the adult rat brain and improved motor function. A small number of cells stained for either astrocytic or neuronal markers (Mahmood, Lu, Wang, & Chopp, 2002), but were far too few to provide cellular replacement. This group also reported that i.v. administration of MSCs 1 day after brain injury in the rat brain resulted in an increase in BDNF and NGF (Mahmood et al., 2002). Both intracerebral and i.v. MSC administration promoted endogenous progenitor cell proliferation after traumatic brain injury (Mahmood, Lu, & Chopp, 2004), and functional recovery was dose dependent and persisted for at least 3 months (Mahmood, Lu, Qu, Goussev, & Chopp, 2006). Recently another group confirmed the therapeutic effect of human MSCs (hMSCs) in a rat model of TBI and demonstrated that expression of neurotrophic growth factors was induced by MSC treatment (H. J. Kim, Lee, & Kim, 2010). Furthermore, they observed an increase in phosphorylation of the cell survival signaling molecule, Akt, followed by decreased caspase-3 activation. These results suggest that the therapeutic effects of hMSCs transplantation may involve promotion of antiapoptotic activity as a result of secreted growth factors (H. J. Kim et al., 2010).

A single Phase I study using bone marrow-derived MSCs in children after isolated TBI has recently been completed (Cox et al., 2011). In this study, 10 children age 5–14 years with a Glasgow coma scale score of 5–8 were treated with 6 × 106 bone marrow-derived mononuclear cells per kg body weight delivered intravenously within 48 hours of an isolated TBI. To determine the safety of administration, systemic and cerebral hemodynamics, laboratory parameters, chest radiographs, and serial clinical assessments were monitored. Additionally, serial cerebral magnetic resonance imaging neuropsychologic evaluation, and functional outcome measures were obtained as preliminary measures of efficacy. There were no identifiable adverse events with close monitoring of the neurologic, pulmonary, renal, hepatic, and hematologic systems. Functional and neuropsychological testing, including the Glasgow Outcome Scale, the Pediatric Injury Functional Outcome Scale, and the Wechsler Abbreviated Scale of Intelligence, revealed recovery consistent with (or improved from) expected baselines. Magnetic resonance imaging volumetric data revealed no significant change in grey matter, white matter, intracranial volume, or CSF space at 1 and 6 months as measured relative to expected norms. Authors concluded that bone marrow harvest and intravenous mononuclear cell infusion as treatment for severe TBI in children is logistically feasible and safe.

The therapeutic effect of MSCs was also demonstrated in animal models of stroke. Several recent studies showed that transplantation of MSCs, derived from bone marrow, into rodent cerebral ischemia models can reduce infarct size and improve functional outcome (18,27,50,52,83,85,106,110,111,139,144). MSCs derived from adipose tissue (ADSCs) also showed therapeutic effect in rat model of cerebral ischemia (150). Importantly, treatment of ischemic animals with neurally induced ADSCs resulted in better functional recovery and more reduction in hemispheric atrophy in comparison to unmodified ADSCs (150).

To test the clinical relevance of these observations, recently, a phase I clinical trial was conducted. A feasibility and safety of transplantation of autologous human MSCs in stroke patients was the main objective of this trail (51). In this study the autologous MSCs were delivered intravenously 36–133 days post-stroke. All patients had magnetic resonance angiography to identify vascular lesions, and magnetic resonance imaging prior to cell infusion and at intervals up to 1 year after. Neurological status was scored using the National Institutes of Health Stroke Scale and modified Rankin scores. The results of this study showed that the median daily rate of National Institutes of Health Stroke Scale change was 0.36 during the first week post-infusion, compared with a median daily rate of change of 0.04 from the first day of testing to immediately before infusion. No central nervous system tumors, abnormal cell growths or neurological deterioration was observed, and there was no evidence for venous thromboembolism, systemic malignancy or systemic infection in any of the patients following stem cell infusion. Thus the stroke is another potential target for MSCs therapy.

4.2 MSCs in neurodegenerative diseases

There is currently a great deal of interest in the use of MSCs to treat several neurological diseases such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and multiple sclerosis.

Recently, a number of studies have examined the ability of MSCs to differentiate into dopamine-producing cells, re-innervate the striatum, and ameliorate behavioral deficits in Parkinsonian models. Varying degrees of success have been achieved in vitro, including dopaminergic marker expression, and dopamine secretion in response to depolarization (Dezawa et al., 2004; Fu et al., 2006; Guo et al., 2005; Suon, Yang, & Iacovitti, 2006; Trzaska, Kuzhikandathil, & Rameshwar, 2007; Trzaska & Rameshwar, 2011). In addition, engraftment and functional improvement were demonstrated following transplantation of undifferentiated (Hellmann, Panet, Barhum, Melamed, & Offen, 2006; Y. Li et al., 2001) and neurally differentiated MSCs (Dezawa et al., 2004; Fu et al., 2006) in hemiparkinsonian rodents. However, only relatively low efficiencies of dopaminergic differentiation were achieved, and comparisons between the varying methods have not been performed, resulting in difficulties with identifying the optimal methodology. These studies suggest that complex mechanisms might underline the therapeutic effect of MSCs in these animal parkinsonian models and neuroprotection could be the most important ones (P. H. Lee & Park, 2009). Despite all these promising data several issues remain to be resolved including the optimal method for inducing a dopaminergic phenotype from MSCs, engraftment and survival capabilities of MSCs, optimal sites for transplantation, potential immunological responses to MSC grafts, and whether neural differentiation prior to transplantation provides engraftment advantages.

Unlike Parkinson disease, which is a slower degenerative disease and affects a specific area of the brain, amyotrophic lateral sclerosis (ALS) presents quite a challenge for cellular therapy because of the distributed cell loss throughout the body and the requirement to properly reinnervate muscle tissue. Transplantation of wild-type BM cells into irradiated SOD1 transgenic mouse models of ALS demonstrated a delay in disease onset and an increase in life span (Corti et al., 2004). Minimal neural differentiation was detected, thus the authors concluded that functional improvement was likely due to trophic effects. Another study showed that transplantation of human MSCs into SOD1 ALS mice significantly delayed disease onset and progression, in addition to increasing lifespan (56). The human cells survived more than 20 weeks in the xenogenic model, and were able to migrate into the brain and spinal cord and differentiate into neuroglial cells (Zhao et al., 2007). Initial clinical studies began in 2003, when Mazzini et al took autologous MSCs from seven ALS patients and expanded them in culture (Mazzini et al., 2003). The cells were directly transplanted into the spinal cord, and did not result in toxicity or uncontrolled proliferation. Three months after transplantation, four patients experienced a mild reduction in muscle strength decline in the lower limbs. In a long term follow-up of the patients, the same group reported, after 36 months, that four of the seven patients showed a significant reduction in the linear decline of lung function and ALS functional rating scale (Mazzini et al., 2006). Though these preliminary clinical studies are encouraging, further studies are warranted.

Research on the role of MSCs in Alzheimer's disease (AD) is in its infancy. However, a recent study showed positive results in an AD rat model (Wu, Li, Feng, & Wang, 2007). Transplantation of BM-derived MSCs into the hippocampus of rats injected with ß amyloid protein to mimic AD demonstrated significant improvement based on the Morris Water Maze test (Wu et al., 2007). The authors suggested that the MSCs transdifferentiated into cholinergic cells and improved the cognitive ability of the AD rat models. Another group recently showed that transplanted MSCs exerted anti-apoptotic effect in an acutely-induced AD mice model produced by injecting Abeta intrahippocampally (J. K. Lee, Jin, & Bae, 2010). The same group also showed that intracerebral transplantation of BM-MSCs into APP/PS1 mice significantly reduced amyloid beta-peptide (Abeta) deposition (J. K. Lee, Jin, Endo, et al., 2010). Interestingly, these effects were associated with restoration of defective microglial function, as evidenced by increased Abeta-degrading factors, decreased inflammatory responses, and elevation of alternatively activated microglial markers. Furthermore, APP/PS1 mice treated with BM-MSCs had decreased tau hyperphosphorylation and improved cognitive function. Thus, BM-MSCs can modulate immune/inflammatory responses in AD mice, ameliorate their pathophysiology, and improve the cognitive decline associated with Abeta deposits. These results demonstrate that BM-MSCs are a potential new therapeutic agent for AD. Interestingly, Stroch A. et al and his group recently detected the functional induction of two genes upon neuroectodermal conversion of human adult MSCs, namely F-spondin and neprilysin (CD10), with a 4,992 + or - 697-fold and 692 + or - 226-fold increase of mRNA levels in converted cells compared to MSCs, respectively (Habisch et al., 2010). These genes are known to be involved in the formation and degradation of Abeta peptides, respectively. Consistently, co-incubation of the neuroectodermally converted MSCs with HEK-293 cells stably expressing amyloid precursor protein (APP) lead to a significant cell dose-dependent decrease of Abeta peptides. These in vitro results indicate that neurally modified MSCs might be even more

useful vehicles for delivering anti-Abeta activity and thus exhibiting the maxium therapeutic effect on AD (Habisch et al., 2010).

The potentials of MSCs as a therapy for autoimmune neurological diseases arose from some unexpected observations. Therapies with MSCs were originally based on their similarities to most adult stem cells and the possibility that they might regenerate tissues through their ability to differentiate into mesodermal tissues and perhaps other embryonic lineages. The unexpected observation that MSCs inhibited T cell proliferation both in vitro (Di Nicola et al., 2002) and in vivo (Bartholomew et al., 2002b) introduced the possibility that MSCs might be effective in experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis (MS) halting the (auto)immune attack to myelin antigens and promoting nervous tissue repair through their integration in the central nervous system (CNS). During the last few years, animal experiments in the EAE mouse model of MS showed that intraventricular, intraperitoneal or intravenous injection of human or murine BM-MSCs significantly improved clinical outcomes (Bai et al., 2009; Gordon et al., 2008; Kassis et al., 2008; Zappia et al., 2005; J. Zhang et al., 2005) (Zappia et al., 2005, Bai et al., 2009, Gordon et al., 2008, Zhang et al., 2005, Kassis et al., 2008). Chopp's group, in addition to observing functional recovery in EAE mice, demonstrated that small percentage of transplanted MSCs was integrated and expressed neural markers (J. Zhang et al., 2006). Their observations therefore suggested that some transdifferentiation had occurred. Overall, these pioneer studies demonstrated the therapeutic efficacy of MSCs in a model of CNS autoimmunity, but they left open the question whether their integration in the nervous system was essential for their therapeutic benefits.

Recently, a phase I trial was initiated to evaluate the safety and feasibility of intrathecal injection of autologous BM-MSCs in MS patients (Karussis et al., 2010). The initial findings of this trial support the possibility of migration of MSCs from their site of injection (lumbar area of the cerebrospinal fluid) to the brain ventricles and spinal cord parenchyma. Preliminary data of this trail also demonstrated the immunomodulatory effect of MSC in human neurological diseases. The authors concluded that the early clinical stabilization and improvement in some of the patients could be related to these immunomodulating effects. The possibility of neuroprotection and neuroregeneration through transdifferentiation of MSCs into cells of the neuronal or glial lineage, although theoretically viable, has yet to be proved by neuroimaging studies.

Promising results from this study will support further clinical trials to evaluate the long term safety and the potential clinical efficacy of MSC transplantation in the treatment of MS.

5. Conclusions

Although the curative effect of MSCs has been demonstrated in several animal models of CNS injury and neurodegeneration as well as in early human clinical trials of neurological disorders, the mechanisms that are responsible for these beneficial therapeutic effects are still poorly understood. Analysis of accumulated literature in this area suggest the following main mechanisms that may underlie the therapeutic effect of naive or neurally modified MSCs: 1) neurorepair (replacement of damaged or diseased neural cells by neurally transdifferentiated MSCs), 2) neuroprotection (modulation of immune response and inflammation, provision of trophic factors that could prevent neural cell apoptosis and

demyelination); 3) neuroregeneration (creation of a favorable environment such as cellular bridges, guiding strands and scaffolds, provision of of neurotrophines, growth factors or cytokines that could promote axonal growth and sprouting and endogenous neurogenesis, restoration of blood flow, repair of blood–brain barrier, angiogenesis). However, these mechanisms are not mutually exclusive and it is most likely that combination of several factors accountable for such therapeutic effects.

6. References

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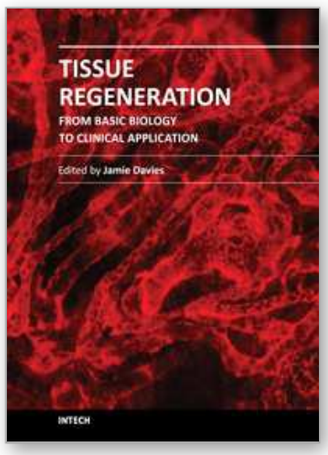

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When most types of human tissue are damaged, they repair themselves by forming a scar - a mechanically strong 'patch' that restores structural integrity to the tissue without restoring physiological function. Much better, for a patient, would be like-for-like replacement of damaged tissue with something functionally equivalent: there is currently an intense international research effort focused on this goal. This timely book addresses key topics in tissue regeneration in a sequence of linked chapters, each written by world experts; understanding normal healing; sources of, and methods of using, stem cells; construction and use of scaffolds; and modelling and assessment of regeneration. The book is intended for an audience consisting of advanced students, and research and medical professionals.

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