

# Mesenchymal Stromal Cells and Neural Stem Cells Potential for Neural Repair in Spinal Cord Injury and Human Neurodegenerative Disorders

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## 1. Introduction

Spinal cord injury represents a serious neurodegenerative condition mostly characterized by inflammation, demyelination, loss of neurons and glial cells. Patients who suffer from spinal cord trauma show limited functional recovery, which frequently leads to deficit of multiple sensory, motor and autonomic systems resulting to clinical signs of partial or complete paralysis with prominent spasticity and rigidity (Cizkova et al. 2007). Because of the limited regenerative capacity of the adult CNS due to the inhibitory molecules, decrease of trophic factor support and scar tissue formation, the current functional treatments for SCI are not successful (Rowland et al. 2008). However, emerging research evidences on regenerative medicine involving adult and neural stem cells has put much attention on the development of cell based therapies which could promote regeneration of lesioned CNS (Barnabe-Heider & Frisen, 2008; Goldman, 2005). One of the most important factors for the stem cells candidates that are being used in transplantation strategies, is their compatibility with the host tissue. Therefore, preferential criteria for stem cells transplantation in clinical trials are their ability to be used as autologous transplant to avoid moral and ethical dilemma as well as immunosuppressive therapy. Mesenchymal stem cells (MSCs) fulfill all these criteria and can be easily isolated from patient's bone marrow or adipose tissue. However, in many cases their beneficial effect in regard to the treatment of neurodegenerative disorders is most likely due to paracrine (Zacharek et al. 2007) or immunomodulatory effects (Djouad et al. 2003), rather than by direct cell replacement (Jorgensen, 2009). Therefore, other sources of autologous stem cells, such as „Schwann cells“ derived from peripheral nerve, „Olfactory ensheathing cells“ (OECs) (Papastefanaki et al. 2007; Raisman et al. 2011) from olfactory bulb, or even allogenic

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embryonic or neural stem cells have been involved in different studies to replace lost/impaired neural population. Particularly, rapidly improving neural stem cells (NSCs) research has been providing encouraging evidence that stem cells derived from nerve tissue can repair CNS structure and perhaps even function which is impaired by various neurodegenerative disorders. NSCs that can self-renew, are multipotent cells committed to generate a neural phenotype, thus making them easier to differentiate into the desired sources of neuronal or pro-oligodendroglial cells that may be applied for further transplantation strategies. The accuracy of both autologous vs allogenic cell based approaches was confirmed in recent studies where application of adult and neural stem cells into injured spinal cord or to a wide variety of neurodegenerative diseases led to improvement of functional outcome in animal models through replacement of damaged or dead motor neurons and thereby remyelination of spared axons and modulation of inflammation (Louro & Pearse, 2008; Kim & de Vellis, 2009; Nandoe Tewarie et al. 2009). As with any cell therapy in CNS, it is important to realize that more complex issues need to be considered, such as: the selection of cell source, effective delivery strategies, optimal dosing of stem cells, proper timing and safety guarantees of stem cells based treatment.

Here we have tried to outline the most important basic issues of MSC, NSC research in regard to their therapeutic potential to repair or enhance plasticity in neurodegenerative disorders, with main focus on SCI. The following sections summarize the MSCs and NSCs fundamental biological properties, their potential sources and perspective advantages in cell-based therapies.

## **2. Mesenchymal stem cells**

Mesenchymal stem cells, also called bone marrow stromal cells represent a heterogeneous population of the cells derived from the non-blood forming fraction of bone marrow . They are able to differentiate into bone, tendon, cartilage and fat (Pittenger et al. 1999) or under specific condition into neuronal, muscle, liver cells (Keilhoff et al. 2006; Yu et al. 2007; Greco & Rameshwar, 2008) as well as epithelial cells of lung, skin, kidney and gastrointestinal tract (Herzog et al. 2003). The first evidence for the existence of non-hematopoietic stem cells derived from bone marrow has been available from Friedenstein's work in 1970s (Friedenstein et al. 1976). Friedenstein isolated cells from bone marrow and plated them on plastic culture dish. After 4 hours, he removed the medium with non-adherent cells (mostly containing hematopoietic stem cells) and observed that a small number of cells with spindle-shape morphology remained adhered to the Petri dish and form foci of two or four cells. After the 2-4 days, the adherent cells started to multiply and attained spindle-shaped morphology (Friedenstein et al. 1976). From a physiological point of view, MSCs represent a major population of bone marrow stromal cells, that by the continuous release of EPO (erythropoietin-EPO) and granulocyte-colony formation stimulating factor (granulocyte colony stimulating factor G-CSF), promote survival, division and differentiation of hematopoietic precursor/stem cells (Cui et al. 2009). Since then non-hematopoietic stem cells have been identified in many other organs and tissues including skin, skeletal muscle, teeth, adipose tissue, testis, gut, liver and ovarian epithelium (Kerkis et al. 2006; Guan et al. 2006; Zuk et al. 2002).

## 2.1 Isolation of MSCs from bone marrow and adipose tissue

MSCs can be isolated by aspiration of bone marrow from the diaphysis of the tibia or femur in rats, mice, which represent only 0,001-0,01% of the total population of nucleated cells (Pittenger et al. 1999). In humans, bone marrow derived MSCs (BM-MSCs) are mainly obtained from superior iliac crest of pelvis (Digirolamo et al. 1999). *In-vitro* cultivation of MSCs is very simple because of their plastic adherence, their extensive proliferative capacity and ability to create single-cell-derived colonies (Colter et al. 2000). There is a possibility for MSCs exploitation in autologous transplantations to prevent immunological response or rejection of implanted cells. Compared to embryonic stem cells, MSCs have reportedly low tumorigenic potential and they are capable to migrate toward tumors (Loebinger et al. 2009) and into the sites of neural lesions (Chen et al. 2008). Another source of mesenchymal stem cells represents the adipose tissue. Adipose tissue-derived mesenchymal stem cells (AT-MSCs) are also multipotent, plastic adherent, have similar CD markers as BM-MSCs and under specific condition they are able to differentiate into cells of the mesodermal, osteogenic, chondrogenic, adipogenic and myogenic lineages and even into cells with neuron-like morphology (Zuk et al. 2002). Moreover, isolation of AT-MSCs is easier (by liposuction); less painful and number of obtained cells is much higher in comparison to BM-MSCs (Lin et al. 2008). In spite of this, MSCs obtained from bone marrow represent the main source of stem cells in preclinical and clinical studies until now.

### 2.1.1 Morphology and phenotype of MSCs

According to the morphology, MSCs are classified into two groups: spindle-shaped type, also called very small rapidly self-renewal round cells (RSCs) (Colter et al. 2001) and flattened type (Mets & Verdonk, 1981) known as a mature MSCs (mMSCs). RSCs are characterised by rapid rate of replication after low density plating, potential for multilineage differentiation and by the presence of specific cell surface epitopes which are not found at mMSCs stage, such as: vascular endothelial growth factor receptor-2 (FLK-1), TRK (a nerve growth factor receptor), transferrin receptor and annexin II (lipocortine 2) (Colter et al. 2001). Unlike, mMSCs are characterised by large-scale and flatted morphology, lower property of replication and higher ratio of cytoplasm-to-nucleus when compared to RSCs. Moreover, MSCs express several positive cell surface molecules that allow us to distinguish them from the hematopoietic stem cells such as:  $\beta$ -integrins (CD29), CD44,  $\alpha$ -integrins (CD49a, CD49b), CD61, P-selectin (CD62), CD90 (thy-1), CD105, CD106 (VCAM-1) and CD166 (Majumdar et al. 2003; Docheva et al. 2007), collagen type I and IV, laminin, fibronectin; chemokine receptors: CXCR5,6-R, CCR1,7,9-R; CX3CL1-R; growth factor receptors: TGF $\beta$ -R, PDGF-R, NGF-R, FGF-R; and cytokine receptors: IL1,3,4,6,7,15-R, TNF $\alpha$ -R (Dominici et al. 2006; Stagg, 2007). The immune phenotype of cultured MSCs is described as MHC class I+, MHC class II-, CD40-, CD80- and CD86-. This phenotype is regarded as non-immunogenic and suggests that MSCs might be effective in inducing tolerance (Javazon et al. 2001). It has been documented that during aging, MSCs undergo several changes and thereby lose their differentiation capacity and decrease production of specific proteins and factors responsible for cell differentiation such as bone morphogenic protein (BMP-7), alkaline phosphatase, G-CSF (granulocyte colony-stimulating factor), LIF (leukemia inhibitory factor) and stem cell factor (SCF). Moreover, differentiation potential of MSCs is

down regulated from the 6th passage on and the mean length of telomeres is shortened after 9th passage revealing morphological abnormalities typical of the Hayflick model of cellular aging (Bonab et al. 2006). According to these evidences it is very important to realize the fact that mesenchymal stem cells which are applied in regenerative medicine should be used in early passages where currently their rapid proliferation and increased differentiation capacity are utilized.

### 2.1.2 Trophic properties of MSCs

Several reports suggest that application of MSCs in neurodegenerative disorders led to neuroprotective effect and to the replacement of diseased and damaged cells and tissues in the most affected area. Profuse scientific investigations revealed that the main effect of the neuroprotection and neuroregeneration is mediated by specific neurotrophic molecules and cytokines that are directly produced by MSCs. It has been also shown that these factors can support neuronal cell survival and regenerate nerve fibers at the lesion sites (Mahmood et al. 2004). *In vitro* studies have confirmed the presence of various neurotrophic factors produced by MSCs, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF) and neurotrophin-3 (NT-3) (Chen et al. 2005; Kurozumi et al. 2005). Measurement of 56 separate subclones derived from human MSCs showed that differences in neurotrophin's production between single cell clones can vary in a huge range (from 167 to 2000-fold) and expression of these neuro-regulatory molecules was able to promote survival and neurite outgrowth in the SH-SY5Y neuroblastoma cell line. Consecutive selection of the most producing single cell derived clones can lead to better exploitation of MSCs in regenerative and cell replacement medicine (Crigler et al. 2006). Moreover, MSCs also constitutively express several interleukins including IL-6, IL-7, IL-8, IL-11, IL-12, IL-14, IL-15, macrophage or granulocyte-macrophage colony stimulating factor (M-CSF, GM-CSF), stromal cell-derived factor 1 $\alpha$  (SDF-1 $\alpha$ ) (Crigler et al. 2006), Flt-3 ligand and stem cell factor (Majumdar et al. 1998) that can play an important role in immunomodulatory processes.

### 2.1.3 Immunomodulatory effect of MSCs

Recent studies demonstrate that MSCs command with the ability to modulate an immune response depending on the stimulus to which they are exposed. Their dual ability, to suppress and/or activate immune responses, can lead to modulation of the reaction of broad range of immune cells, including T cells, B cells, NK cells and antigen-presenting cells (Stagg, 2007). It is assumed that the main effect of immunosuppression is evoked by soluble factors that are produced by MSCs or immune cells, such as: hepatocyte growth factor, indoleamine 2, 3-dioxygenase (IDO), prostaglandin E2, TGF- $\beta$ 1, nitric oxide and IL10. It has been also observed that MSCs use different mechanisms that are responsible for inhibition of function and proliferation of immune cells (Nauta & Fibbe, 2007). INF $\gamma$  play a crucial role in regulation of MSC-mediated immunosuppression. INF $\gamma$  induce MSCs to release prostaglandins and IDO, which causes depletion of tryptophan, an essential factor for lymphocyte proliferation (Aggarwal & Pittenger, 2005). The similar suppressive effect on T-cell proliferation was also suggested in the presence of TGF- $\beta$  and hepatocyte growth factor, which are constitutively produced by MSCs (Di Nicola et al. 2002). Cocultivation of MSCs

with lymphocytes revealed that MSCs don't constitutively secrete suppressive factors but provide a dynamic cross-talk between MSCs and lymphocytes (Augello et al. 2005). MSCs can interfere with dendritic cells (DCs) differentiation, maturation and function. It has been observed that MSCs had an inhibitory effect on differentiation of monocytes and CD34+ progenitors into CD1a+-DCs by skewing of their differentiation property toward macrophages (Nauta & Fibbe, 2007). At the same time, immature DCs were unable to induce T cells activation in the presence of MSCs. Cocultivation of MSCs with NK cells showed that allogeneic MSCs could inhibit IL-2 and IL-15-induced proliferation of resting NK cells and either MSCs are able to suppress the proliferation and cytokine production of IL-15 stimulated NK cells via soluble factors. Suggesting that there is also the existence of different mechanisms for MSC-mediated NK cell suppression demonstrated experiments where after inhibition of both soluble factors - PGE2 and TGF- $\beta$  produced by MSCs complete restoration of proliferation capacity of NK cells was observed (Sotiropoulou et al. 2006).

### 3. Application of MSCs in neurodegenerative diseases

Transplantation of autologous or allogenic mesenchymal stem cells has been considered as a potential therapeutic approach to a wide variety of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson disease (PD), sclerosis multiplex (SM), amyotrophic lateral sclerosis (ALS), spinal cord injury (SCI) or stroke.

#### 3.1 Utilization of MSCs in therapy for SCI

Traumatic injury to the spinal cord initiates a cascade of reactive changes, which results in permanent damage and loss of neurological function below the lesion site (Rowland et al., 2008). The inflammatory events, together with ischemia, Ca<sup>2+</sup> influx into cells, edema, and progressive hemorrhagic necrosis significantly contribute to secondary injury, which causes progressive cavitation and loss of spinal tissue (Kwon et al. 2010). The expression of adverse neurite growth-inhibitory molecules in the extracellular matrix (Fawcett, 2006; Schwab, 2004) together with lack of trophic factor support and the discontinuity of axonal projections caused by progressive tissue cyst formation pose multifactor obstacles contributing to the loss of spinal cord regeneration and inability to find an effective therapy (Nagahara & Tuszynski, 2011). However, by addressing aspects, such as neutralization of growth inhibitors Nogo-A, CSPGs, delivery of various trophic factors or utilizing stem cells/progenitors, a considerable progress has been made in enhancing the growth of injured adult axons (Bradbury et al. 2002). The widespread use of stem cell therapy has shown that transplantation of MSCs can improve recovery after stroke (Chopp & Li, 2002), promote remyelination (Akiyama et al. 2002), as well as contribute to partial recovery of locomotor function in animal models of spinal cord injury (SCI) (Cizkova et al. 2006) (Sykova & Jendelova, 2005; Arboleda et al. 2011; Forostyak et al. 2011). Thus, achieved progress in animal SCI models utilizing MSCs made it possible for translating preclinical findings to human clinical trials. For example, transplantation of unmanipulated autologous bone marrow in patients with subacute and chronic SCI resulted into improvement of motor/or sensory functions within 3 months. Although, implantation of autologous bone marrow cells appears to be safe, it is necessary to follow up patients outcome data, for more than 2 years (Sykova et al. 2006; Pal et al. 2009; Moviglia et al. 2009). While there is evidence

that MSCs can give rise to cells with neural characteristics *in vitro* (Kim et al. 2002) and *in vivo* (Jendelova et al. 2004), it is more likely that production of neurotrophic or vascular factors (Zhong et al. 2003; Hamano et al. 2000) together with immunomodulatory effects (Aggarwal & Pittenger, 2005) have a dominant influence on recovery of function following spinal cord trauma. Particularly, suggested hypoinflammatory nature of MSCs, imply for unique MSCs immunomodulatory approaches, that could be used for immunosuppression to induce allotransplantation tolerance or even to attenuate autoimmune, inflammatory responses (Le Blanc & Ringden, 2005). Although some experimental studies in animals or pre-clinical human studies demonstrate the effectiveness and safety of MSCs therapy, there are still many questions to be answered regarding the mechanisms of engraftment, homing, inter-cellular interactions, immunological profiles, *in vivo* differentiation as well as long-term safety.

### 3.1.1 MSCs therapy for Parkinson disease

Parkinson disease (PD) is the second most common neurodegenerative disorder in the world characterized by progressive loss of nigrostriatal dopaminergic neurons leading to deficiency of dopamine in striatum which is responsible for control of movement. The characteristic symptoms in patients suffering from PD are rigidity, akinesia, tremor and balance problems (Pechadre et al. 1976). Number of studies investigated whether transplantation of human mesenchymal stem cells (hMSCs) can lead to protective effect on progressive dopaminergic neuronal loss *in vitro* or *in vivo* conditions. Intravenous injection of hMSCs into the PD transgenic rat models showed strong protective effect on progressive loss of dopaminergic neurons in substantia nigra. Human MSCs reduced the caspase-3 activity and increased survival of TH-immunoreactive cells in substantia nigra in comparison with the control group. Moreover, a significant improvement in behavioral motor tests in hMSCs treated group has also been observed (Park et al. 2008). *In vitro* study demonstrated that SDF- $\alpha$ -1, chemokine constitutively produced by MSCs increased dopamine release and led to suppression of cell death induced by 6-OHDA administration compared to untreated group (Wang et al. 2010). Neuroprotective effect of hMSCs on dopaminergic neurons mediated by anti-inflammatory properties of MSCs and their modulation of microglial activation were uncovered (Kim et al. 2009). Transplantation of GDNF-transduced MSCs into the PD animal model supported the evidence, that they are capable to induce a local trophic effect in the denervated striatum and sprouting from remaining dopaminergic terminals toward neurotrophic milieu. Exploitation of new optogenetic technique demonstrated for the first time that intrastrially grafted stem cell-derived dopamine neurons become functionally integrated in the dopamine-denervated striatum (Tonnesen et al. 2011). Noninvasive intranasal delivery of MSCs to the unilaterally 6-hydroxydopamine - lesioned rat brains showed decreasing concentrations of inflammatory cytokines, increasing of tyrosine hydroxylase level in the lesioned ipsilateral striatum and substantia nigra, and prevented any decrease of dopamine in the lesioned hemisphere. Simultaneously, significant improvement of motor function of forepaw in PD rat model was observed (Danielyan et al. 2011).

### 3.1.2 MSCs therapy for Alzheimer disease

Alzheimer disease (AD), the most common form of dementia, is characterized as a progressive neurodegenerative disorder (Berchtold & Cotman, 1998). Degeneration and

dysfunction of the neurons and decline of synaptic function and plasticity mostly in brain regions responsible for memory and learning, as hippocampus, entorhinal cortex, basal forebrain and neocortical association cortices, are the most incident symptoms that generally characterize AD (DeKosky et al. 1996). There is no cure or early preclinical diagnostic assay available for Alzheimer's disease. Currently, most prevalent is symptomatic therapy, which is not able to stop the progression of the disease. Therefore, Alzheimer's disease is still being recognized as an unmet medical need. In 1906, Dr. Alois Alzheimer, identified two specific features that are mostly figured in AD human brain, neurofibrillary tangles and amyloid plaques. Deep investigation in the study of the main structural components responsible for the creation of two pathological hallmarks in AD brain, uncovered inherence of tau protein in NFT and amyloid beta peptide in amyloid plaques. Several years later, it was demonstrated that strong neuroinflammation occurs in AD brain (Novak et al. 1993) (Dickson et al. 1988; Zilka et al. 2006; Zilkova et al. 2006).

Application of stem cells in AD preclinical studies brought in last years several positive results. Taking advantage of stem cells immunomodulatory and trophic properties and their transplantation into AD transgenic animal models showed that they are the most appropriate tool for the achievement of functional restoration of damaged cells and in the same manner for the replacement by healthy one (Blurton-Jones et al. 2009; Hampton et al. 19 2010; Lee et al. 2010). Recent developments in stem cell technology raise the prospect of cell therapy for human neurodegenerative tauopathies. Transplantation of the neural stem cells or administration of mesenchymal stem cells isolated either from human umbilical cord or from the bone marrow has produced beneficial effects in several independent animal models of AD (Blurton-Jones et al. 2009). Above mentioned reports have shown that the neuroprotective effect of stem cells may be mediated 1) by their ability to produce various trophic factors that contribute to functional recovery or 2) by activation of neuroinflammatory pathways. *In vitro* studies show that MSCs can prevent tau mediated cell death in the Alzheimer's cell model. It has been confirmed that MSCs have significant impact on tau cell death cascade and can ameliorate toxic effect of misfolded truncated tau that is considered to be driving force behind neurofibrillary degeneration. Therefore it may be suggested that the cell neuroprotective therapy rather than cell replacement therapy represents prospective strategy for treatment of Alzheimer's disease and related tauopathies (Zilka et al. 2011).

#### 4. Neural stem cells

The human brain contains roughly 100 billion neurons, of which several thousands die every day, representing the loss of millions of nerve cells across the life span. For this reason, it has been believed for a long time, that adult mammalian central nervous system (CNS) is rather rigid structure, unable to repair itself following diseases or injury. However, in some brain regions dead neurons could be replaced and potentially could contribute to the regeneration of damaged nerve tissue (Graziadei & Graziadei, 1979). Therefore, a number of controversial issues concerning possible CNS plasticity was raised and broadly discussed. Finally, in the 1960s and 1970s, most of the uncertainties were addressed and neuroscience's central tenets the 'no new neurons' doctrine, was reconsidered following the key-revolutionary discovery of Joseph Altman (Altman, 1962; Altman & Das, 1965),

documenting thymidine- $H_3$ -labelled neurons and neuroblasts in the adult rat brain. From now on a huge effort has gone into unraveling and understanding the fundamental mechanisms of adult CNS regeneration in mammals.

#### 4.1 Neural stem cells definition and origin

It took almost twenty years of dedicated research involving a large number of scientific experiments which clearly confirmed ongoing neurogenesis not only in songbirds (Nottebohm, 1981), but also in rodents, non-human primates and humans, in whom new imaging techniques, such as bromodeoxyuridin (BrdU) labeling, etc, enabling identification of proliferating cells were applied (Eriksson et al. 1998). All these studies jointly confirmed that new functional neurons are generated in the adult mammalian, including human CNS in two discrete areas: i) in the hippocampus, the subgranular zone (SGZ) of the dentate gyrus, which is an important center of our memory (Gage, 2000; Alvarez-Buylla et al. 2002) and, ii) in subventricular zone (SVZ), representing a thin layer of cells lining along the lateral cerebral ventricles, where a nerve cells essential for olfaction are generated (Gage, 2000; Lledo et al. 2006). In both areas, neurogenesis progresses as a complex multi-stage process, which starts with the proliferation, followed by migration and terminal differentiation (Abrous et al. 2005). The current knowledge of self-renewing and multipotent neural stem cells is largely defined by *in vitro*, as well as *in vivo* evidences documenting their ability to generate the main progeny of the nervous system: neurons, astrocytes and oligodendrocytes (Gage, 2000). NSCs reside in specific anatomical microenvironments that are called neurogenic niches; small islands where neurons and glial cells are continuously generated (Doetsch et al. 1999). However, neurogenic regions (SVZ, SGZ) must meet following criteria: 1) contain neural precursors (NPCs) that are generated in, 2) neurogenic niches, providing cell-cell contacts and diffusible factors for terminal neural differentiation, and 3) provide neurogenic potential (thus, ability of NPCs that are implanted in a neurogenic areas to generate neurons, while when implanted into other brain location they give rise to glia). Another interesting pool of neural precursor cells is represented by astrocytes found within the germinal layers of the adult brain. It has been broadly documented that these astrocytes retain the stem cell properties throughout the life span, and are involved in both neuro- and gliogenesis (Alvarez-Buylla et al. 2001; Gotz & Huttner, 2005; Mori et al. 2005).

##### 4.1.1 Neurogenesis mediated by pathological conditions; Properties of non-neurogenic areas

Normal adult neurogenesis produces a limited number of newly generated functional cells that primarily serves to maintain physiological tissue homeostasis in specific CNS systems. Initially, the neurogenic processes have been expected to be rather stable, moreover insensitive to external stimuli. However, this view has been changed, due to the growing evidence documenting that SVZ and SGZ are responding to a various local or global signals generated from nerve tissue damage. For example, neurogenesis in both neurogenic zones is increased in animal experimental models of ischemia/stroke (Zhang et al. 2008) as well as in humans suffering from stroke (Curtis et al. 2007), epileptic seizures (Grote & Hannan, 2007) and multiple sclerosis (Nait-Oumesmar et al. 2007). Furthermore, neurogenesis is increased

in human cases and animal models of Huntington's disease while it is reduced in Alzheimer's and Parkinson's disease as well as in depression and stress (Elder et al. 2006; Grote & Hannan, 2007). Stem cells with the potential to generate new neurons that could replace dying neurons in neurodegenerative diseases or CNS injuries reside also in other areas of the adult CNS, indicating to the possibility that endogenous sources of NSCs can be mobilized also from non-neurogenic regions (Minger, 2007). These NSCs have been demonstrated in brain areas such as septum, striatum or even in the spinal cord, but so far it was not clearly established whether these stem cells are capable of differentiation to the final functional neurons (Liu & Martin, 2003; Wiltrout et al. 2007). Furthermore, it has been suggested that ependymal cells (ECs) adjacent to the SVZ of the lateral ventricles, may mimic the characteristics of NSCs (Johansson et al. 1999; Doetsch et al. 1999). A study by Coskun et al. (Coskun et al. 2008) documented that this may be the case, because the subpopulation of ependymal cells, CD133+/CD24-, exhibited features of quiescent NSCs *in vitro*, i.e., self-renewal and multipotency as well as participation in neurogenesis *in vivo* after injury. In this relation, the occurrence of ependymal cell layer covering CNS ventricular system including the areas around the third, fourth ventricles, and the central canal (CC) of the spinal cord supports suggestion, that also these regions may retain similar quiescent NSCs as those which were identified in the lateral ventricles (Weiss et al. 1996).

#### 4.1.2 Neurogenic potential in the spinal cord and stimulatory factors

There is increasing evidence that the CC ependymal cell region, which is regarded as presumptive neurogenic area of adult spinal cord, contains a limited number of neural stem cells. Once implanted in the animals, they differentiate into oligodendrocytes and astrocytes (Mothe & Tator, 2005) while, under *in vitro* conditions, they give rise to both neurons and glia (Yamamoto et al. 2001). On the other hand, neuronal or glial fate of grafted ECs is highly depended on the host neurogenic/non-neurogenic microenvironment (Shihabuddin et al. 2000). These contradictory findings are often explained in regard to beneficial (*in vitro*) or inhibitory (*in vivo*) conditions directly influencing neuronal or glial fate (Weiss et al. 1996). Furthermore, after pathological condition such as spinal cord injury, most of the newly dividing intrinsic ependymal stem cells migrate toward damaged tissue, where they develop into macroglial cells, while only few cells retain primitive nestin-like phenotype (Johansson et al. 1999; Cizkova et al. 2009a). Likewise, a significant number of neural progenitors could be activated also in other regions of the parenchyma (Horner et al. 2000) (Kehl et al. 1997). However, it remains unclear whether these progenitors develop into functional neurons.

A stimulatory effect on spinal progenitors may be obtained also after physiological stimulation, when experimental animals are exposed to an enrichment environment or physical activity. Previous experiments have shown that mice providing systematic exercise in a running wheel had twice more new hippocampal neurons than controls (Gomez-Pinilla et al. 2001). Beside this, it has been confirmed that voluntary exercise can increase levels of brain-derived neurotrophic factor (BDNF) and other growth factors, which stimulate neurogenesis, improve learning, mental performance (Gomez-Pinilla et al. 2001) and may mobilize gene expression profiles that could be beneficial for CNS plasticity processes (Neeper et al. 1995). These data were further confirmed in latter studies showing that enhanced physical activity in adult rats induces an endogenous ependymal cell response leading to increased proliferation, although in more attenuated manner if compared with

SCI (Cizkova et al. 2009b) (Fig.1). Indeed, there is one group of studies that favor the fact that ECs might contribute to *de novo* neuronal differentiation following CNS injury (Ke et al. 2006; Danilov et al. 2006), while others refuse this suggestion (Zai & Wrathall, 2005). Based on these findings, it is un-doubtful that the adult spinal cord retain a certain reservoir of neural precursors, which can under various specific conditions stimulate and promote the recovery of injured spinal cord.

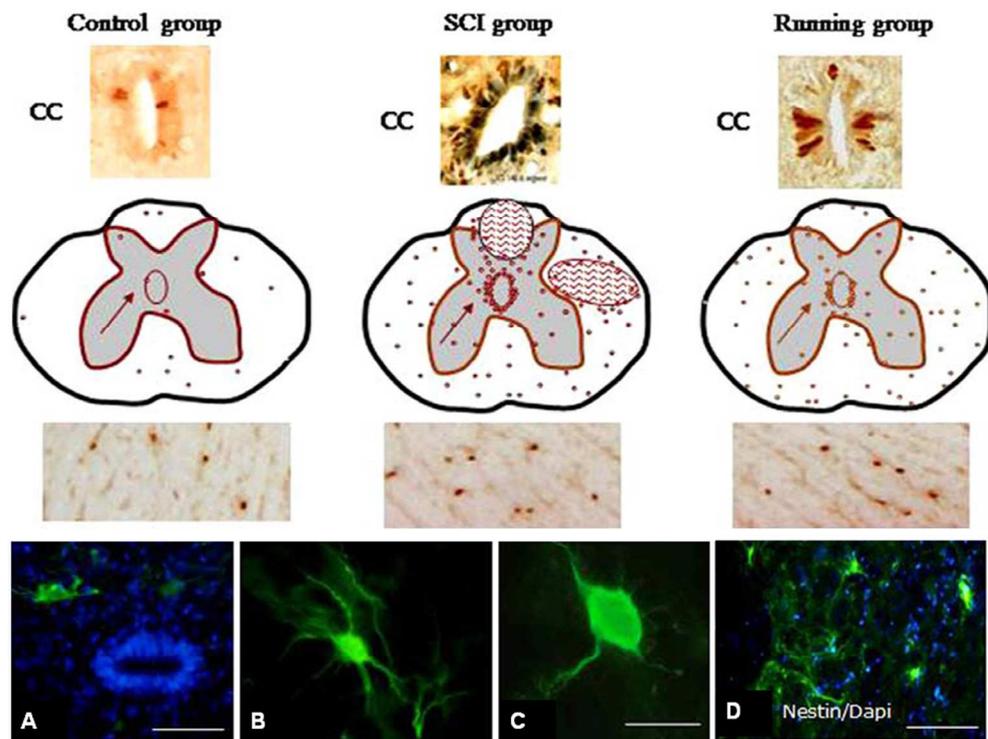


Fig. 1. Schematic illustration of BrdU IR in the thoracic spinal cord section (Th8) of the control, SCI or Running group. Note, the highest BrdU expression in the CC canal, and around the lesion site of SCI group, different distribution patterns of BrdU-positive nuclei in the ependyma between SCI and Running group, and increased BrdU response in the parenchyma of the SC in both groups. Below each schematic drawing, a panel revealing BrdU-IR in the corresponding ventral white matter is performed. (A-D) Fluorescence microscopy images of occasionally occurring nestin-positive cell bodies (green) with processes, found in the close vicinity to the CC gray matter, dorsal horn or adjacent to lesion site.

#### 4.1.3 Molecular mechanisms of neurogenesis

Neurogenesis is understood as a complex process that is regulated by a wide variety of important signaling molecules such as: growth factors, cytokines, and neurotransmitters.

Their primary function is to mediate a balance between proliferation, migration and survival of NSCs within the neurogenic niche. The most important growth factors affecting cell division are: FGF (fibroblast growth factor), VEGF (vascular endothelial growth factor), EGF (epidermal growth factor / epidermal growth factor), PDGF (platelet-derived growth factor) and BDNF (brain derived neurotrophic factor). Therefore, endogenous neurogenesis can be stimulated by intraventricular infusion of mitogenic factors such as EGF, bFGF, TGF $\beta$  (transforming growth factor  $\beta$ ) that stimulate the proliferation activity in the SVZ and thus restore the nervous tissue (Kuhn et al. 1997). Nitric oxide (NO), erythropoietin, bone morphogenetic protein (BMP Bone Morphogenetic Protein) and Wnt proteins (Wiltrout et al. 2007) also play an important role in regulating neurogenesis. BMP and its receptor that are expressed by the SVZ cells promoting differentiation of the NSCs toward glial phenotype are blocked by Noggin, which is produced by ECs and in contrast drives differentiation into neurons (Lim et al. 2000). The most important regulatory neurotransmitters include GABA ( $\gamma$ -aminobutyric acid) and glutamate, which maintain homeostasis of newly formed neurons (Platel et al. 2007). GABA decreases the proliferation of neuroblasts and NSCs, whereas glutamate stimulates their division. It is noteworthy that in all types of damaged nerve tissue which is associated with glutamate excitotoxicity an increased neurogenesis, is documented. GABA is synthesized and released by neuroblasts and activates GABA<sub>A</sub> receptor, causing loss of proliferation of neuroblasts and astrocytes. We can conclude that GABA acts as a negative modulator inhibiting cell division, which means that with increased number of neuroblasts there is a higher amount of released of GABA and more GABA<sub>A</sub> receptors are activated (Bordet et al. 2007).

## 5. Transplantation strategies utilizing NSCs

Neural progenitors isolated from vertebrate central nervous system (CNS) represent valuable source of cells that hold particular promise for treating a variety of human neurological diseases such as spinal cord injury (Goldman, 2005). Due to the pathological events and limited ability of the spinal cord to repair itself, therapeutic approaches are focused either on: i) stimulation of endogenous neuronal plasticity and mobilization of oligodendroglial progenitors (Azari et al. 2005; Fawcett, 2006; Yang et al. 2006) or ii) development of an effective cell selection techniques to gain desired NSCs progeny used for cell-replacement therapy (Faulkner & Keirstead, 2005; Hofstetter et al. 2005; Keirstead et al. 2005). However, an important issue due to the pathological nature of spinal cord damage it is important to select the most convenient strategy involving desired cellular pools for transplantation. For example, spinal ischemia-induced spastic paraplegia which is associated with a selective loss of small inhibitory interneurons, would necessarily involve implantation of neuronal progenitors. On the other hand, diseases or spinal cord trauma, with different pathological outcome, resulting in demyelination of axons followed by destruction of long descending tracts would rather require transplantation of myelin-producing cells such as oligodendroglial cells, Schwann cells or Olfactory ensheathing cells (Keirstead et al. 2005; Keilhoff et al. 2006; Pearse et al. 2007; Raisman, 2007). Since a well-documented repertoire of specific surface markers for cells of NSCs at different developmental stages have been identified, it may be possible to identify factors which affect their commitment to oligodendroglial cells or neurons and combine this with optimal sorting methods (Deng & Poretz, 2003; Pruszek et al. 2007; Uchida et al. 2000). In particular, magnetic cell separation using specific monoclonal antibodies (e.g. A2B5, PSA-NCAM) conjugated to nanoparticles allowing positive retention or negative dilution of

selected cells provide a feasible approach for experimental cell enrichment of desired oligodendroglial progeny, which may be used in future trials for cell-based therapies to treat spinal cord injury (Cizkova et al. 2009a). These studies have shown that MACs technology enable us to gain about a 5 to 9 fold increase of immature, mature oligodendrocytes content (NG2+, RIP+, MBP+) when compared to amount of oligodendroglial cells acquired from unseparated population (Fig.2). A great deal of attention has been given to NSCs isolated from various regions of CNS, including embryonic and adult spinal cord, that could differentiate into desired oligodendrocytes and myelinate host axons in various pre-clinical animal models of SCI (Tarasenko et al. 2007; Kakinohana et al. 2004). For example, NSCs derived from human fetal brain improved recovery after contusion SCI either in severe combined immunodeficiency (SCID) or myelin-deficient shivered mice (Cummings et al. 2005). Highly purified oligodendrocyte progenitors could be generated also from human embryonic stem cells (hESCs) (Nistor et al. 2005; Cloutier et al. 2006). Based on their remyelination properties described in preclinical animal SCI models, the Geron Corporation has initiated a first clinical trial (Phase I) by transplanting hESC-derived oligodendrocyte

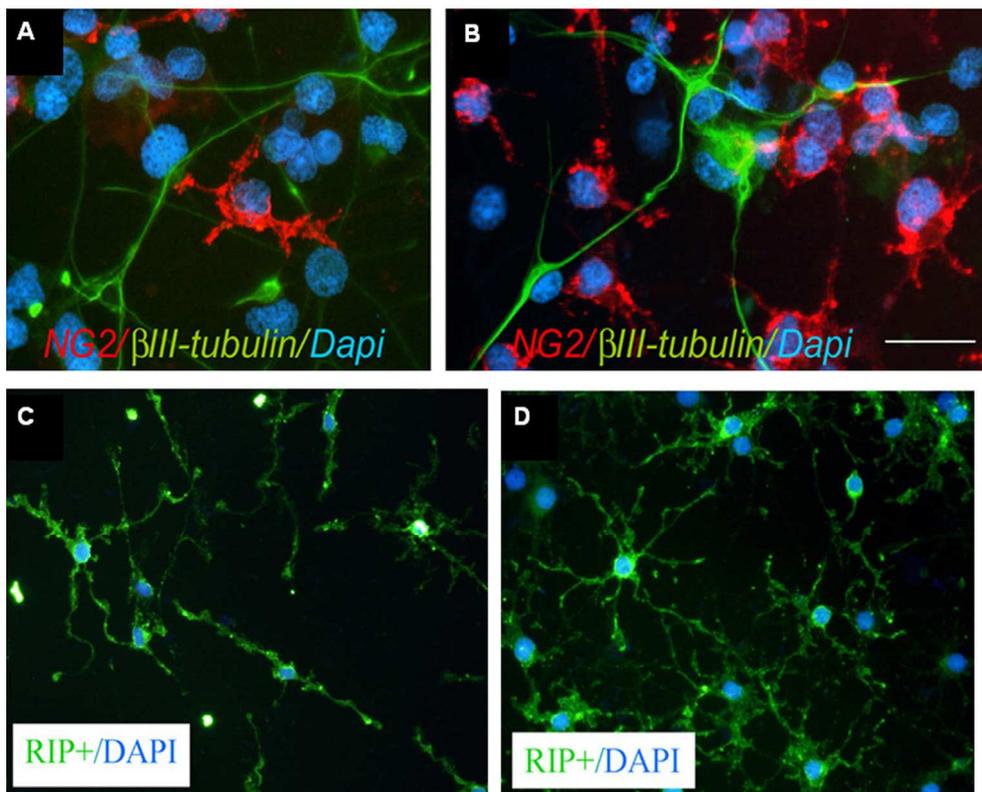


Fig. 2. Immature neurons expressing  $\beta$ III-tubulin (green) occurred in both, unseparated (A) and separated NSC population (B), but higher number of immature NG2+ oligodendrocytes (red, A, B) and mature RIP+ oligodendrocytes (green C, D) was found after MACs (B, D) (compare A with B and C with D).

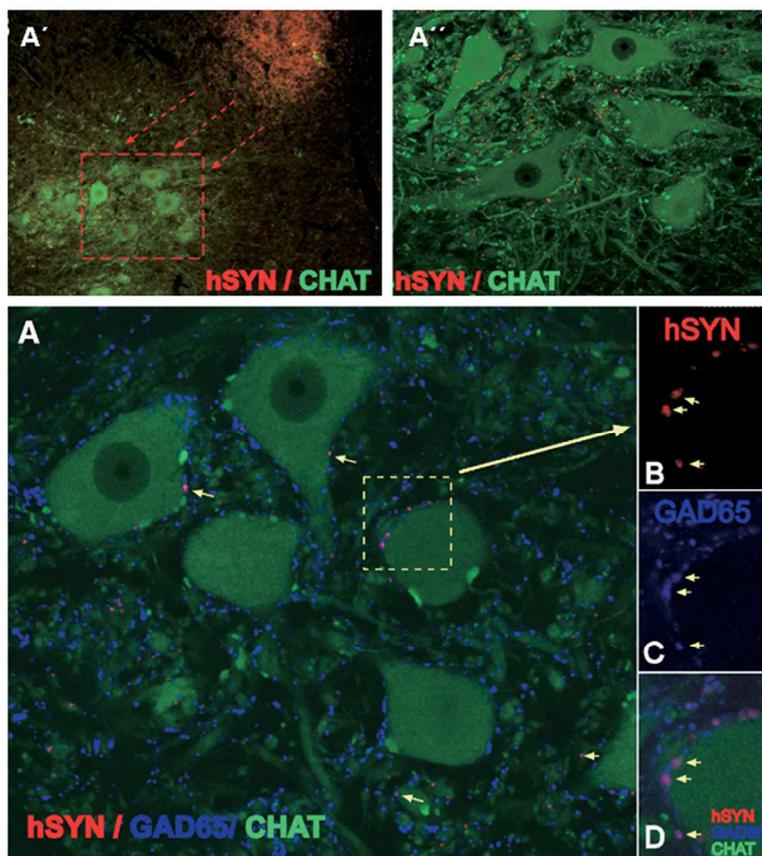


Fig. 3. Fluorescent microscopy images (A', A'') and single confocal optical images (A-D) of transverse spinal cord sections taken at 3 months after grafting and stained with human specific hSYN antibody (B, red), CHAT antibody (A, green) and GAD65 antibody (C, blue) antibodies. The majority of hSYN terminals showed co-localization with GAD65 (B-D, yellow arrows).

Progenitor cells in patients with spinal cord injuries. Their preliminary data showed a very good safety profile, with no serious adverse events, no evidence of cavitation at the injury site and no immune responses to the transplanted cells even after complete withdrawal of immunosuppression. One of the most important properties of NSCs is their ability to generate functional neurons, which could potentially rebuild altered local neuronal network following spinal injury. Thus, implanting NSCs-derived neuronal pools in animals subjected to spinal ischemia-induced paraplegia, where selective loss of small local inhibitory interneurons, with persisting  $\alpha$ -motoneurons occurs, could meet the needs and expectations to reconstruct impaired local inhibitory neuronal circuits. Although, the precise mechanism leading to spastic paraplegia and rigidity is not certain, the neuropathological features of a selective degeneration of GABA, GAD immunopositive inhibitory neurons are well defined. In addition, the loss of these specific inhibitory pools localized in the intermediate zone of the

spinal grey matter, ultimately leads to an increase in the monosynaptic reflex and near-complete loss in spinal polysynaptic activity. A challenging study done in collaboration with anesthesiology research laboratory at University of California San Diego, has shown that NSCs derived from human fetal spinal cord grafted into a rat model of ischemic spastic paraplegia resulted into a progressive recovery of motor function with correlative improvement in motor evoked potentials (Cizkova et al. 2007). Of note, transplanted NSCs became integrated into host neuronal circuits and displayed an extensive axo-dendritic outgrowth and active rostrocaudal/dorsoventral migration for about 8-12 weeks. Furthermore, intense hSYN immunoreactivity was identified within the grafts and in the vicinity of persisting  $\alpha$ -motoneurons. These hSYN immunoreactive synaptic terminals expressed GAD65 immunoreactivity in 40-45% of human grafted cells, referring to their inhibitory fate (Fig. 3). All together, these data conclude that functional recovery was associated with long term survival of grafted neurons with GABAergic phenotype that most probably contributed to suppression of spasticity (Cizkova et al. 2007). Similarly, human hNT neurons (teratocarcinoma cell line) or rat spinal neuronal precursors (SNPs), grafted into ischemic spinal segments depleted of inhibitory neurons, restore local inhibitory tone and ameliorate spasticity (Marsala et al. 2004). In addition, when human derived NSCs were treated with a cocktail of growth factors and later transplanted into the injured spinal cord, they differentiated preferentially into cholinergic neurons (Wu et al. 2009). Although, it seems that NSCs are a powerful source of neural progenitors that are constitutively secreting a variety of growth stimulating factors (NGF, BDNF, GDNF), they are often genetically modified to further enhance their potential and secrete additional factors such as neurotrophin 3 (NT-3), or are combined with antibodies that neutralize ciliary neurotrophic factor (CNTF), in an attempt to attenuate astrocytic differentiation (Ishii et al. 2006).

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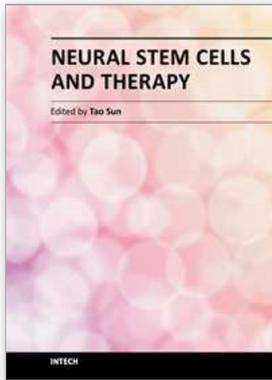
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This book is a collective work of international experts in the neural stem cell field. The book incorporates the characterization of embryonic and adult neural stem cells in both invertebrates and vertebrates. It highlights the history and the most advanced discoveries in neural stem cells, and summarizes the mechanisms of neural stem cell development. In particular, this book provides strategies and discusses the challenges of utilizing neural stem cells for therapy of neurological disorders and brain and spinal cord injuries. It is suitable for general readers, students, doctors and researchers who are interested in understanding the principles of and new discoveries in neural stem cells and therapy.

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