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Human mesenchymal stem cells in the treatment of neurological diseases

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Here we provide a comprehensive data on the unique features of mesenchymal stem cells (MSCs) which makes them feasible and preferred candidate for cell-based therapy in neurological clinic. From this point of view the most important features of these cells are: (1) availability from autologous sources independently from age of patient; (2) extensive expansion *in vitro*; (3) immunomodulatory "bystander" function after transplantation *in vivo*; (4) potentiality to protect, repair or eventually replace impaired or dysfunctional host cells. For complete these last task of functional regeneration of central nervous system, we have to take advantages of MSCs capability for transient, time-locked proliferation, migration to site of injury and their commitment to neuronal differentiation. However, if we are to make progress in the use of MSCs for therapy in the clinic it will be necessary to establish more unified, advanced standards for cells processing *in vitro* as well as safer and improved procedures for their delivery *in vivo*.

Key words: mesenchymal stem cells, neurological diseases, cell transplantation

INTRODUCTION

Mesenchymal stem cells (MSCs) are multipotent, fibroblast-like cells that were first found in stromal compartment of bone marrow then described in 1970s by Friedenstein (Friedenstein et al. 1976). In addition to bone marrow, similar populations have been identified in others adult and fetal tissues including: bone and adipose tissue, skeletal muscle, teeth, pancreas, lung, liver, amniotic fluid, cord blood and umbilical cord tissues (UC) (Campagnoli et al. 2001, Lee at al. 2004, da Silva Meirelles et al. 2006). MSCs are defined as a heterogeneous cell population which can be isolated by exploiting their plastic adherence and then expanded *in vitro*. The cells display capability for self-renewal and differentiation into all lineages of mesodermal origin, including bone, cartilage and fat cells. There are also evidences showing that MSCs are capable to differentiate into cells originating from other than mesodermal sources such as neurons, hepatocytes or epithelial cells (Woodbury et al. 2000, Hermann et al. 2004). This could be explained by contribution of the very early set of MSC clones (the waves) appearing during embryogenesis and derived either from a neuroepithelium (Takashima et al. 2007) or a cranial neural crest (Ishii et al. 2012). These cells display pluripotent characteristic and can give rise to different ectomesenchymal derivatives, including smooth muscle, neurons, glial cells or endothelium (Santagati et al. 2003). Even if this population is only transient, restricted and then replaced by MSC derived from mesodermal sources, it can contribute to observed heterogeneity of the fraction, at least to the part derived from immature, fetal tissues. Under *in vitro* conditions they can differentiate and express among other also the neural markers like nestin or β-tubulin III (Tondreau et al. 2004, Minguel et al. 2005). On the other hand there is also well documented data that in heterogeneous population of adult stem cells homing into the MSC niches there is a subset of primitive stem cells identified by different isolation methods. They are cells of so called the side population (SP), multipotent progenitor cells (MAPCs), marrow-isolated adult multilineage inducible cells (MIAMI), very small

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embryonic-like stem cells (VSEL), the lineage-depleted FR25Lin- cells or endothelial progenitor cells (EPC) (Goodell et al. 1996, Jiang et al. 2002, Amrani and Port 2003, D'Ippolito et al. 2004, Kucia et al. 2006, Goldenberg-Cohen et al. 2012). Due to their pluripotent features they may contribute in various degrees to lineage of MSC differentiation. To consolidate that extremely heterogeneous results the International Society of Cellular Therapy (ISCT) defined three basic criteria essential for MSC characteristic: (1) plastic-adherence in cell culture, (2) positive expression of et least three surface membrane molecules CD73, CD90, CD105 together with negativity in respect of the hematopoietic markers like CD14, CD34, CD45 and human leukocyte antigen DR (HLA-DR) and (3) ability to osteo-, adipo- and chondroblastic differentiation *in vitro* (Horwitz et al. 2005, Dominici et al. 2006).

The MSCs attract a lot of attention in the context of their usefulness for the cell based therapies. In general such therapies may be associated with either direct replacement of damaged cells by exogenously implanted MSC or indirectly, by their support to endogenous regeneration. Numerous recent data demonstrated successful use of mesenchymal stem cells in hematology, cancer therapy and various acquired or inherited genetic diseases (Qiao et al. 2008, Markert et al. 2009, Bitsika et al. 2012, Chao et al. 2012). The therapeutic potential of these cells has been demonstrated in experimental treatment of numerous neurological diseases and neural tissues injuries (Miller et al. 2010, Momin et al. 2010). Accessibility of autologous MSC, their immunomodulatory and trophic properties and ability to multi-lineage differentiation makes from these cells the most valuable resource for regenerative medicine and tissue engineering (Pittenger et al. 1999, Kastrinaki et al. 2008, Locke et al. 2009). For clinical therapies MSCs could be isolated from different sources, including bone marrow, peripheral blood and different after-birth tissues. Recently also adipose tissue has been considered as a good alternative source for MSC isolation. Fat is an abundant and very easily accessible tissue, rich in adipose-derived mesenchymal stem cells (A-MSCs) that possess, beside of others also proneural differentiation capacity as well as paracrine properties, all features required for their regenerative applications (Fraser et al. 2006, Gimble et al. 2007).

Differentiation potential of MSC

As described above MSCs can differentiate into variety of different tissues (Fig. 1) being descendants of the mesodermal but also the other primary germ layers.

Several investigators have reported that different types of MSCs can differentiate into neuronal-like phenotypes under permissive conditions (Jeong et al. 2004, Bae et al. 2011, Claros et al. 2012, Ferroni et al. 2012). Positive results in neural differentiation were obtained with the use of different experimental protocols, for example by treating cells with chemical compounds, growth factors or co-culturing them with neurons or other cells in tree-dimensional cultures. Studies of Sanchez-Ramos, Storch and Woodbury groups shown that mesenchymal stem cells derived from bone marrow (BM) change their phenotypes and acquire neural-like features *in vitro* (Sanchez-Ramos et al. 2000, Woodbury et al. 2000, Storch et al. 2002). In these experiments researchers have confirmed neuronal MSC differentiation observing expression of nestin, GFAP, neurofilament M, neuN and neuron-specific enolase and other neural markers. Results obtained by Tondreau and coworkers (2004) shown that 80% of BM-MSC spontaneously express immature neural markers even at most early stages of culture. In later stages, these cells acquired even more matured neural-like phenotypes and expressed markers characteristic for mature neurons and astrocytes, i.e. MAP2 and GFAP. Also Alessandri and colleagues (2004) reported in human skeletal muscle-derived stem cells (SkmSCs) a subpopulation with MSC-like characteristics that can differentiate into neural phenotype. Under special permissive conditions these cells acquire neural features revealed the expression of β-tubulin III, GFAP and nestin (Alessandri et al. 2004,

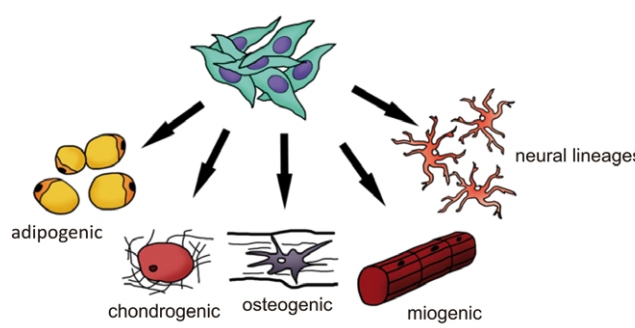

Fig. 1. Multilineage differentiation of mesenchymal stem cells

Canzi et al. 2012). Moreover, mentioned before differentiation of adipose tissue-derived MSC or WJ-MSC toward neurons and glial cells has been described (Gimble et al. 2007, Ferroni et al. 2012).

Yet, other researchers negated the authenticity of neural differentiation of MSC and suggested that acquirement of the neural-like morphology resulted rather from stress-connected artifactual cell overstaining than from genuine neural differentiation (Woodbury et al. 2000, Lu et al. 2004, Neuhuber et al. 2004, Bertani et al. 2005). Clarifying this question would be especially important for answering if potential uses of these stem cells could be broadened to accommodate, in addition to indirect neuroprotective and immunomodulatory effects, also to classical cell replacement strategy (Jablonska et al. 2010). Our own results obtained for MSC derived from human umbilical cord Wharton jelly support ability of these cells to spontaneous neural differentiation (Fig. 2). Also other immature human tissues, like umbilical cord blood mononuclears (Habich et al. 2006) or their derivatives can display similar neural differentiation potential (Buzanska et al. 2002, Zychowicz et al. 2012) confirmed not only by immunocytochemical and molecular cell characteristic but also by direct electrophysiological data (Sun et al. 2005, Jurga et al. 2009)

Paracrine activity of MSCs

Beside the ability to multilineage differentiation, preclinical studies indicated that MSCs secrete plethora of the important growth factors, cytokines and extracellular matrix compound that can enhance cell survival in the damaged tissues (Li et al 2002, Schinkothe et al. 2008, Li et al. 2010). These supportive effects of MSC have been experimentally tested in various animal models of main neurological disorders including stroke, Parkinson's Huntington's diseases (PD and HD), ALS (amyotrophic lateral sclerosis), AD (Alzheimer's disease) and SM (sclerosis multiplex) (Zebardast et al. 2010, Wen et al. 2011).

Another recently explored mechanism responsive for supportive role of MSCs in tissue regeneration may involve, in addition to classical paracrine activity, a partial cell fusion (direct cell-to-cell connection), which would lid to direct exchange of intracellular components. This interaction is based on the formation of thin membrane channels (tunneling nanotubes), which can combine neighboring cell membranes. It has been reported that mesenchymal stem cells and cardiomyocytes can exchange their cytoplasmic components, organelle and parts of membranes thought such nanotube structures (Acquistapace et al. 2011). This intercellular transport may play significant role in regeneration process but still needs further investigations (Cselenyak et al. 2010).

Recently, it has been described the other mechanism utilizing formation of microvesicles (MVs) which can be involved in cell-to-cell communication. MVs are plasma membrane exosomes released by various cell types including mesenchymal stem cells and their progenitors. MVs may deliver various proteins, mRNA, miRNA and bioactive lipids affecting the function of target cells (Schorey et al. 2008). MVs receptor-mediated transfer of these macromolecules may facilitate exchange of information between cells and influence various processes including reprogramming and differentiation. Proteomic analysis of human MSCs derived MVs revealed that they contain approximately around 730 proteins associated with cell cycle, proliferation, differentiation and self-renewal signaling pathways. Obtained results allowed identification among these MVs various protein molecules belonging to surface receptors (PDGFRB, EGFR, and PLAUR),

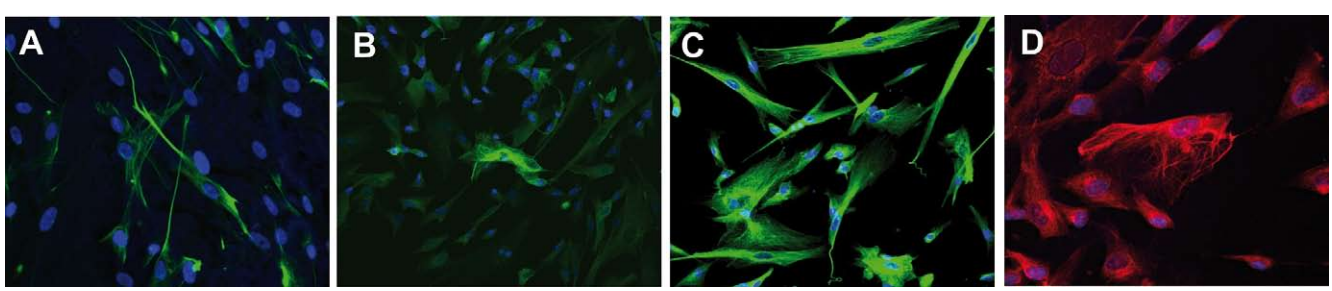

Fig. 2. Expression of neural markers in WJ-MSC (Wharton jelly mesenchymal stem cells) cultured under standard conditions. Part of the cells at 4–5 passage can spontaneously express nestin (A, green), NF200 (B, green) patches of βIII-tubulin (C, green) and GFAP (D, red). Nuclei were counterstained by Hoechst (blue).

components of Wnt, MAPK, BMP, TGFβ, PPAR signaling pathways, cell adhesion proteins and MSC-associated antigens (Kim et al. 2012). Bruno and coworkers (2009) demonstrated that bone marrow mesenchymal stem cells produce MVs containing special mRNA which have exerted a beneficial effect on repair processes in acute kidney injury. Moreover, Collino and colleagues (2010) have recently shown that MVs from BM-MSC contain selected patterns of miRNA involved in cells survival, proliferation and differentiation or lineage specification which can be used as signature of these cells origin. MVs can transport either endogenous or synthetic miRNA to neighbor cells and may regulate expression profile of many specific genes.

MSC immuno-modulatory functions

The unique and most valuable property of mesenchymal stem cells is connected with their potential immunomodulatory function. It is known that MSCs can influence severity of the innate as well as acquired immune reactions. This property make them valuable for the clinical treatment of several autoimmune syndromes including multiple sclerosis (MS) (Djouad et al. 2009, Fiorina et al. 2009, Gonzalez-Rey et al. 2010) and graft-*versus*-host disease (GVHD) (Bartholomew et al. 2002, Nauta and Fibbe 2007).

Several unique features of MSC were implicated as responsible for their immunomodulatory potential. Firstly, MSC were shown to express vestigial amounts of the major histocompatibility complex MHC class I and MHC class II molecules together with co-stimulatory CD80, CD40, CD86 markers (Tse et al. 2003, Le Blanc and Ringden 2007). This property indicates that transplanted MSCs are non-immunogenic and thus able to avoid host immune attack even when implanted without immunosuppression (Spaggiari et al. 2008). MSCs can also modulate activation and proliferation of T and B lymphocytes (Corcione et al. 2006, Yang et al. 2009, Duffy et al. 2011) and alters their secretion profiles. They promote a strong anti-inflammatory T helper 2 (Th2) response and inhibit deteriorating pro-inflammatory T helper cell type 1 (Th1) response. Moreover, secreted by MSCs macrophage-colony-stimulating factor (M-CSF) and IL-6 may interfere with the differentiation and functionality of brain residing dendritic cells (DC) (Djouad et al. 2007). Specifically, the MSCs caused mature DCs type 1 (DC1) to decrease tumor necrosis factor α (TNF-α) secretion and mature DC2 to increase interleukin-10 (IL-10) secretion; MSCs caused Th1 cells to decrease interferon γ (IFN-γ) and caused the Th2 cells to increase secretion of IL-4; MSCs caused an increase in the proportion of regulatory T cells (T_{reg}) to more tolerant phenotype and decrease secretion of IFN-γ from the natural killer (NK) cells. Numerous studies have confirmed that infused MSCs mobilize endogenous stem cells to migrate from their tissue niches as well as from the recipient bone marrow and then directed them into injured and inflamed areas where they contribute to described above anti-inflammatory effects (Wakabayashi et al. 2010, Sheikh et al. 2011).

Migratory properties of MSC

Several studies have shown that MSCs have ability to migrate toward the injured tissues in response to variety of endo/paracrine signals that attracts them directly in the receptor-mediated manner (Spaeth et al. 2012). Mechanism of MSCs migration involves expression of the numerous specific receptors and ligands to facilitate their trafficking, adhesion and infiltration into pathogenic microenvironment. Among actually described migratory axis there are chemokine receptors molecules like CCR1-4, CCR7-10, CXCR1-6, CXCR4 and a broad range of cell surface adhesion antigens like β1-integrins (CD29), VEGFR, CD44 and their local ligands CXCL12 (SDF-1) or VEGF (Ponte et al. 2007, Brooke et al. 2008, Wang et al. 2008, Yu et al. 2010). In addition there are many others guiding axis of cell migration which exact homing mechanism is still under intensive investigation. Several experimental approaches are directed toward enhance of the natural cell tropism into targeted brain regions. They include overexpression of tissue factors affecting cell migration like metalloproteinases, statins and adhesion molecules which modifies cell migratory behavior in response to endogenous guidance cues. Also *ex vivo* treatments of MSCs with cytokines (Pasha et al. 2008, Choi et al. 2010), their genetic modification (Kurozumi et al. 2004, Nomura et al. 2005) or hypoxic-ischemic MSCs preconditioning (Grayson et al. 2007) before transplantation is expected to improve MSCs migration. Other observation indicated that G-CSF treatment can mobilize endogenous MSC populations of bone marrow and increase their quantity in peripheral blood and migration toward injured cerebral tissue

Table I

The summary of published results of clinical trials concerning MSC application in the most common neurological disorders

Neurological disease	Route of delivery	No. of cases	Tx cell No.	Main findings	Comments	Reference
Stroke acute phase	i.v.	treated group – 5 untreated group –25 MSC	5×10^7 two doses	Side effects: no serious adverse events Clinical outcome: trend towards increased functional recovery	1 year follow-up	Bang et al. 2005
	i.v.	treated group – 16 untreated group – 36 MSC	5×10^7 two doses	Side effects: no serious adverse events Clinical outcome: trend towards increased functional recovery	5 years follow-up	Lee et al. 2010
	i.a. (MCA)	treated group – 20 BM MNC	15 ml one dose	Side effects: no serious adverse events Clinical outcome: increased functional recovery	0.5 year follow-up 40% patients showed a good clinical outcome	Friedrich et al. 2012
	i.a. (MCA)	1 case BM MNC	3.0×10^7 one dose	Side effects: no serious adverse events Clinical outcome: not reported	8 hours follow-up 1% of tx cells were labeled with Tc^{99m} labeling with Tc^{99m} is a feasible noninvasive method	Correa et al. 2007
chronic phase	i.v.	treated group – 6 untreated group – 6 MSC	$5–6\times10^7$ one dose	Side effects: no serious adverse events Clinical outcome: trend towards increased functional recovery	0.5 year follow-up tx cells were suspended in serum-free media all patients were rehabilitated for 8 weeks	Bhasin et al. 2011
	i.v.	treated group – 20 untreated group – 20 MSC	$5–6\times10^7$ one dose	Side effects: no serious adverse events Clinical outcome: trend towards increased functional recovery	0.5 year follow-up	Bhasin et al. 2012
	i.v.	treated group – 12 MSC	$0.6–1.6\times10^8$ one dose	Side effects: no serious adverse events Clinical outcome: not reported	1 year follow-up tx cells were suspended in autologous human serum	Honmou et al. 2011
	i.a. (MCA)	treated group – 6 BM MNC	$1.25–5\times10^8$ one dose	Side effects: no serious adverse events Clinical outcome: not reported	4 months follow-up 2×10^7 cells were labeled with Tc^{99m} whole body scintigraphy indicated cell homing in the affected hemisphere at 2 h, while the remaining uptake was mainly distributed to liver, lungs, spleen, kidneys and bladder.	Barbosa et al. 2010

Table I (cont.)

The summary of published results of clinical trials concerning MSC application in the most common neurological disorders						
Neurological disease	Route of delivery	No. of cases	Tx cell No.	Main findings	Comments	Reference
Cerebral pulsy	i.v.	one case MSC	4×10^7 four doses	Side effects: no serious adverse events Clinical outcome: trend towards increased functional recovery	1 year follow-up	Li et al. 2012
Global brain ischemia	intra-ventricular	one case UCB MNC neutraly committed	3.6×10^7 three doses	Side effects: no serious adverse events Clinical outcome: trend towards increased functional recovery	3 years follow-up	Jozwiak et al. 2010
Traumatic brain Injury (TBI)	intra-parenchymal i.v.	treated group – 7 MSC	1st dose 10^7–10^9 2nd dose 10^8–10^{10}	Side effects: no serious adverse events	0.5 year follow-up	Zhang et al. 2008
Spinal cord injury (SCI)	intra-thecal	treated group – 30 MSC	1×10^6/kg one dose	Side effects: no serious adverse events Clinical outcome: partial improvement	0.5 year follow-up no change in ASIA scale; improvement in Barthel's index	Pal et al. 2009
	i.v.	treated group – 8 MSC	4×10^8 one dose	Side effects: no serious adverse events Clinical outcome: not reported	3 months follow-up	Ra et al. 2011
	intra-spinal intra-dural i.v.	treated group – 8 (4 acute, 4 chronic) MSC	4×10^8 one dose	Side effects: no serious adverse events Clinical outcome: partial improvement	2 year follow-up improvement in quality of life and bladder function	Geffner et al. 2008
	i.a. i.v.	treated group – 20 (7 acute, 13 chronic) MSC	10^4–5.3×10^8 one dose	Side effects: no serious adverse events Clinical outcome: varied outcome	1 year follow-up 5 patients treated i.a. showed improvement	Sykova et al. 2006
	intra-spinal intra-dural	treated group – 10 MSC	8×10^6 (spinal cord) one dose or 1st dose 4×10^7 (spinal cord) 2nd dose 5×10^7 (lumbar tapping)	Side effects: no serious adverse events Clinical outcome: varied outcome	0.5 year follow-up 3 patients showed gradual improvement in activities of daily living, in MRI decreases in cavity size and the appearance of fiber-like low signal intensity streaks	Park et al. 2012

Table I (cont.)

The summary of published results of clinical trials concerning MSC application in the most common neurological disorders

Neurological disease	Route of delivery	No. of cases	Tx cell No.	Main findings	Comments	Reference
Spinal cord injury (SCI)	intra-spinal	treated group – 35 untreated group – 13 MSC	2×10^8 one dose	Side effects: no serious adverse events Clinical outcome: small increase in acute treatment no significant improvement was observed in the chronic treatment	10 months follow-up additionally i.v. GM-CSF was administrated AIS grade increased in 30.4% of the acute and subacute treated patients	Yoon et al. 2007
	intra-spinal	MSC	three increasing doses	Side effects: no serious adverse events Clinical outcome: no significant improvement	patients with chronic SCI	Bhanot et al. 2011
	intra-spinal	treated group – 9 BM HSC	not described	Side effects: no serious adverse events Clinical outcome: increased functional recovery	1 year follow-up improvement from ASIA A to ASIA B,C	Deda et al. 2008
	intra-spinal	treated group – 8 BM MNC	5×10^8–1×10^9 one dose	Side effects: no serious adverse events Clinical outcome: increased functional recovery from ASIA A to ASIA D	treatment combined with rehabilitation	Moviglia et al. 2009
	intra-spinal	treated group – 297 BM MNC	not described	Side effects: no serious adverse events Clinical outcome: varied outcome	follow-up 1–3 years motor improvement in 32.6% atients	Kumar et al. 2009
Parkinson disease (PD)	intra-ventricle	treated group – 7 MSC	1×10^6 /kg one dose	Side effects: no serious adverse events	1–3 years follow-up	Venkataramana et al. 2010
Amyotrophic Lateral Sclerosis (ALS)	intra-spinal	treated group – 10 MSC	$11.4–120\times10^6$ one dose	Side effects: minor adverse effects: pain (n=7), localized sensory impairment (n=5), localized tingling sensation (n=1)	2 years follow-up	Mazzini et al. 2010
	intra-spinal	treated group – 9 MSC	57×10^6 one dose	Side effects: minor adverse effects: transient pain (n=4), transient sensory disturbances (n=6)	4 years follow-up	Mazzini et al. 2008
	intra-spinal	treated group – 19 MSC	57×10^6 one dose	Side effects: no serious adverse events Clinical outcome: no clear clinical benefits were detected	9 years follow-up	Mazzini et al. 2012
	intra-thecal intra-thecal + i.v.	treated group – 19 MSC	$23.4–54.7\times10^6$ one dose	Side effects: minor adverse effects: dyspnea (n=1), fever (n=11), headache (n=5) Clinical outcome: trend towards improvement	follow-up ≥25 months the mean ALSFRS score remained stable during the first 6 months	Karussis et al. 2010

Table I (cont.)

The summary of published results of clinical trials concerning MSC application in the most common neurological disorders						
Neurological disease	Route of delivery	No. of cases	Tx cell No.	Main findings	Comments	Reference
Amyotrophic Lateral Sclerosis (ALS)	intra-ventricle via the Ommaya reservoir	one case MSC	1×10^6 /kg one dose	Side effects: no serious adverse events Clinical outcome: trend towards improvement	cells were tx in autologous CSFrepetitive injection of stem cells is easy and reliable	Baek et al. 2012
Multiple Sclerosis (MS)	intra-thecal	treated group – 10 MSC	8.73×10^6 one dose	Side effects: iatrogenic meningitis (*n*=2), headache (*n*=9) Clinical outcome: varied outcome	26 months follow-up EDSS unchanged (*n*=4), worsened (*n*=5), improved (*n*=1), MRI showed no change (*n*=7), increased lesion (*n*=2), decreased lesion (*n*=1)	Mohyeddin et al. 2007
	intra-thecal	treated group – 10 MSC	$32–100\times10^6$ one dose	Side effects: encephalopathy, seizure Clinical outcome: varied outcome	clinical improvement (*n*=6) worsening of MRI (*n*=2)	Yamout et al. 2010
	intra-thecal intra-thecal + i.v.	treated group – 15 MSC	$24.5–63.2\times10^6$ one dose	Side effects:, aseptic meningitis (*n*=1), fever (*n*=10), headache (*n*=10) Clinical outcome: functional improvement	follow-up ≥25 months reduction of EDSS	Karussis et al. 2010
	i.v.	treated group – 10 MSC	1.6×10^6 /kg one dose	Side effects: no serious adverse events Clinical outcome: improvement in visual acuity and visual evoked response latency	10 months follow-up	Connick et al. 2012
Multiple System Atrophy (MSA)	i.a. i.v.	treated group – 33 MSC	4×10^7 one dose	Side effects: no serious adverse events Clinical outcome: trend towards increased functional recovery	1 year follow-up i.a. infusion resulted in small ischemic lesions on MRI	Lee et al. 2012

(Deng et al. 2011). The other way to enhance the local MSCs penetration toward side of injury is dependent on the mode of cell application. The used in our laboratory the intra-arterial delivery of transplantation material allows avoidance of the first pass effect after cell infusion what gained recently substantial attention (Pendharkar et al. 2010, Gornicka-Pawlak et al. 2011, Lundberg et al. 2012, Osanai et al. 2012).

Clinical applications of MSC

Mesenchymal stem cells have been the first type of stem cells exploited in clinical regenerative medicine owing to their capacity to multipotent differentiation and the feasibility of autologous transplantation. Experimental and preclinical data gave successful results by showing that injection of MSC exerts positive effect on variety of acute and slowly progressive diseases (Newman et al. 2009). Mesenchymal stem cells seem to be promising tools especially for therapeutic application in incurable neurological disorders however precise mechanism of their protective action is still unclear

There are at least three main hypotheses explaining the role of MSCs in neural repair: (1) the ability of these cells to transdifferentiate toward genuine neural lineage and thus to replace damaged cells in the brain tissue, (2) the possibility of fusion between transplanted MSCs and endogenous recipient cells what would change their fate and (3) the capacity of MSCs to release a wide range of trophic factors influencing neurogenesis and enhancing tissue regeneration. The first assertion implies that transplanted cells would be able to differentiate into the distinct types of neural cells *in vivo* and then to integrate functionally with neuronal circuits. It would relay on the induction and promotion of specified neural lineages guided by changes of cell epigenetic programs and gene expression profiles (Choong et al. 2007, Filip et al. 2008). However, as already being discussed, the ability of human MSCs to differentiate toward neural cell fate is still unproven, rare and questioned phenomenon.

In regard to the second option, in the past several studies implicated spontaneous fusion between transplanted mesenchymal stem cells and host neural cells. Ying and Terada demonstrated that MSCs derived from bone marrow fuse with other cell types and acquire the phenotypic properties of those cells (Terada et al. 2002, Ying et al. 2002). In Crain's study the cells derived from bone marrow were transplanted to a female patient. Fluorescent *in situ* hybridization (FISH) connected with radiolabeling showed the fusions between donor and host cells (Crain et al. 2005). In spite of this observation, spontaneous fusion, if really happen, would be a very rare and uncommon phenomenon which cannot explain observed benefits from MSC therapeutic transplantations.

Currently, there are accumulating data suggesting that the third hypothesis may be the most relevant. It seems that MSCs likely promote cellular re-growth, differentiation and survival by secreting plethora of both soluble and insoluble factors like cytokines, growth factors and extracellular matrix proteins (Nakayama et al. 2003, Crigler et al. 2006). Neuroprotective effect can be mediated by secretion of nerve growth factors (NGF) (Cho et al. 2010), brain-derived neurotrophic factor (BDNF) or insulin-like growth factor-1 (IGF-1) (Wakabayashi et al. 2010). All of them can stimulate endogenous regeneration, axonal sprouting and improve neurobehavioral functions. Moreover, concomitantly released angiogenic cytokines like vascular endothelial growth factor (VEGF) (Toyama et al. 2009) and angiopoietin-1 (Ang-1) (Onda et al. 2008, Toyama et al. 2009) may promote neovascularisation in the regenerating tissues.

To understand growing role of MSC in therapy of various acute, traumatic as well progressing neurodegenerative diseases, we must remember that all of these different types of CSN insults can generate a common spectrum of the secondary pathological responses. In all of these pathologies primary insult evokes a local inflammation with reactive astrogliosis, macrophages influx and secondary cell death with connected progression of tissue damage and glial scar formation. Local or systemic MSCs supply might be equally useful in targeting and ameliorating all of these adverse pathological events. From already gathered preclinical data it seems that in the vast majority of tested clinical situations released by MSC trophic factors and bioactive substances suppress effectively neuroinflammation, decrease local lesions and then lighten the symptoms of neurological functional deficits (Table I).

The growing number of clinical investigations addressing MSC-based neuroprotective and immunomodulatory therapeutic abilities are currently designed and tested in different clinical centers (Uccelli et al. 2011). Below we will address them briefly.

In stroke, being one of the most common causes of severe neurological disabilities, the therapy is focused mainly on pharmacological neuroprotection, regeneration of lesioned tissue and physical rehabilitation of the victims. In accordance, in various animal models of local and global cerebral ischemic injuries it has been demonstrated that intravenous infusion of bone marrow derived MSCs can substantially enhance functional recovery due to released neurotrophins and anti-apoptotic factors (Li et al. 2002, Chen et al. 2003, Iihoshi et al. 2004, Jablonska and Lukomska 2011). Basing on these promising results several trials verifying feasibility, safety and efficacy of a cell-based therapy are currently ongoing in various clinical centers (see ClinicalTrials.gov) and the first results are already published (Table I). In majority of them autologous MSC were injected intravenously (Bang et al. 2005) although in cerebral palsy the intraparenchymal and intraventricular brain administrations have been tested as well (Zhang et al. 2008, Chen et al. 2012). Such direct intra-cerebral cell transplantation enables better selection of the injection site which would be achieved under MRI guidance (Correa et al. 2007, Barbosa et al 2010, Jozwiak et al. 2010), assuring the proper cell migration and the optimal concentration of the transplanted cells and protective cytokines and growth factors. The majority of studies carried over the last 1 up to 5 years, reported enhancement of functional recovery, especially when transplantation was combined with intense rehabilitation programs. Furthermore, there were no reported cases of deaths, serious adverse events or stroke recurrence in comparison to the untreated group (Table I).

Stem cell therapy becomes now a reality for treatment of acute spinal cord injury (SCI) (Lee et al. 2007). The efficacy of the therapies using different types of adult stem cells (OECs, MSCs or BM-HSCs) as well as the selection of the best cell transplantation techniques (intradural or intraspinal injection) have been continuously tested in variety of already finished or running trials (Table I). To ameliorate recovery some investigators combined the MSCs treatment with delivery of bioactive molecules together or not with physical rehabilitation of patients (Yoon et al. 2007). Autologous mesenchymal stem cells have also been probed in the therapy of chronic SCI patients (Moviglia et al. 2009). Although many groups confirmed positive effects achieved by these therapies (Deda et al. 2008) in both, acute as well as chronic SCI, the benefit that comes from the early post-injury treatment is unquestionable (Sykova et al. 2006, Kumar et al. 2009).

Amyotrophic Lateral Sclerosis (ALS) is the second most common neurological disorder in which stem-cell-based therapy is currently applied. This is incurable and devastating disease that targets preferentially motoneurons but also the other cellular components of CNS tissue. Mesenchymal stem cells, when applied locally, can modulate this pathological microenvironment in the manner that protects existing motoneurons by referred above, "bystrander" mechanism, involving release of the variety of cytokines and grow factors. The therapeutic cells usually are delivered intraparenchymally into spinal cord or in the brain motoneuron-rich regions or in less harmful manner by the lumbar intra-thecal infusions. Since in this later case, injected cells would sink downward rather than climb up to achieve lesioned brain/stem regions, some groups (Baek et al. 2012) introduced them into ventricular system *via* an Ommaya reservoir. Unfortunately, and despite of promising expectations based on the results from animal experiments (Forostyak et al. 2011, Uccelli et al. 2012), the vast majority of ongoing clinical trials (Chen et al. 2012, Mazzini et al. 2012) showed rather discouraging results. In spite of the only minor adverse effects, such as transient pain, fever, headache or dyspnea, the most of authors did not notice any meaningful clinical improvement after the treatment (Mazzini et al. 2010).

In contrast to these scarcely reported benefits for ALS patient MSC-based therapy of multiple sclerosis (MS) seems to be much more promising. Multiple sclerosis is an autoimmune, slowly-progressing neurodegenerative disease caused by infiltration of the autoreactive T cells crossing the blood-brain barrier and triggering a cascade of pathological, inflammatory reactions (Compston and Coles 2008, Courtney et al. 2009). Currently, treatment of MS relays mainly on immunosuppression combined with monoclonal antibodies and steroid therapies. The immunomodulatory effects induced by MSCs transplants might thus undercurrent therapeutic benefits observed in treatment of EAE (the experimental allergic encephalomyelitis, a classical animal model of the disease), as well as in MS patients. Preclinical experiments have confirmed that immunosuppression mediated by MSCs may lead to inhibition of lymphocytes proliferation, reduction of associated inflammation and protection of axons in the involved areas (Gerdoni et al. 2007, Kassis et al. 2008).

Karussis and coauthors (2010) demonstrated increased number of regulatory T cells and decreased proliferation of lymphocytes at 24 hours after intrathecal or intravenous MSCs transplantation. Unfortunately, along with the introduction of the most effective intrathecal MSC administration, several adverse side effects, such as iatrogenic meningitis (Mohyeddin et al. 2007), encephalopathy, seizures (Yamout et al. 2010) and fever (Karussis et al. 2010) started to be noticed.

For Parkinson's as well as Huntington's neurodegenerative diseases (PD and HD) the cell replacement therapy has been encouraged in the past by promising results reported after transplantation of neural tissues obtained from *post-mortem* embryos (Lindvall at al. 2004). This reports evidenced possibility of functional restoration of the diseased, degenerating human brain. Unfortunately, during following *post-mortem* studies performed at 10 years after the first transplantations, Li and colleagues (2008) described the α-synuclein-positive Lewy bodies being classical hallmarks of neurodegeneration, in the engrafted donor neurons. This observation has questioned the paradigm of a real cell replacement by showing, that the disease can be propagated from the host pathological microenvironment to the engrafted cells. Furthermore, it is also apparent, that recently reported by Venkataramana and others (2010) substantial functional improvement and long-term (3 years) period safety after autologous BM-MSCs transplantation, would be rather a matter of "bystander" neuroprotective effects than the direct replacement of the degenerated neurons.

Due to its fatal prognosis, Huntington's disease (HD) is considered as another preferential target for experimental stem cell-based therapy. Preclinical experiments demonstrated that autologous transplantation of bone marrow stem cells can substantially ameliorate dysfunction and reduce disease-connected memory deficits in animal model of HD (Lescaudron et al. 2003, Jiang et al. 2011). Moreover, delivery of glial derived neurotrophic factor (GDNF) or brain derived neurotrofic factor (BDNF) has been shown to increased neuronal survival and reduce neurological symptoms of the disease (Kells et al. 2004, Gharami et al. 2008). Therefore, researchers invented to combine both of these protective factors by using genetically engineered and neurotrophin over-expressing MSCs as a vehicle to deliver these cytokines directly into damaged tissue (Olson et al. 2012, Sadan et al. 2012). In spite that the obtained effects which confirmed substantial advantages of this strategy in HD animal models, similar therapies have never been yet performed in the clinic.

Alzheimer's disease (AD) is a devastating neurodegenerative systemic disorder characterized by a progressive loss of neurons and synapses in different brain regions. In the effect of systemic dysfunction of mainly cholinergic transmission a steady decline of memory and cognitive brain function is observed and victims become demented and die prematurely. To date, the therapy in AD is only palliative and involves mainly the drugs designed to increase cerebral acetylcholine levels. Thus, MSCs therapy becomes a very attractive option, the more so as their substantial effectiveness has been already confirmed in studies on animals. Interestingly, the most effective mode of treatment, resulting in the extension of the lifespan, reduction of Aβ levels and β-amyloid related pathology consisted i.v. infusion of human cord-blood derived mononuclear cells (Ende et al. 2001, Nikolic et al. 2008, Darlington et al. 2012). Also good results have been obtained by combination of BM-derived mononuclear transplantation with concomitant i.v. administration of various protective small molecules like lipoprotein ApoE or cholinesterase inhibitor phenserine (Zeitouni et al. 2008). Although, basing on this encouraging experimental data several clinical MSCs trials were currently designed and registered (ClinicalTrials.gov), none of them yet finished by publication of the results.

Current attempts were also made to introduce mesenchymal stem cells treatments in combination with anti-cancer therapy (Nakamura et al. 2004, Loebinger et al. 2009, Grisendi et al. 2010, Zolochevska et al. 2012) especially in a treatment of malignant brain tumors like gliomas. Glioblastoma is an aggressive primary tumor with poor prognosis and a short patient's survival time below of 1 year. Surgery and chemo- or radio-therapy gives a little profit because of poor tumor availability and drug penetration due to the presence of a blood-brain barrier. Results from preclinical study of Nakamizo et al have shown that indeed MSCs isolated from bone marrow can migrate in preference into the glioma tumor site after their carotid artery infusion (Nakamizo et al. 2005). Thereafter, investigators applied genetically modified MSCs as a vehicle to deliver INF-β (Interferon β) selectively into the tumor. This treatment significantly slow-down growth of gliomas and increased survival of the tumor-bearing mice in comparison to the control group giving a hope for development of similar therapies in human clinic.

CONCLUSIONS

MSCs are a distinct type of somatic stem cells which unique therapeutic properties have been well documented in various animal models and human clinical studies. Basing on these promising data MSCs appear to be reliable and relatively safe supporter of CSN repair processes. However, even if MSCs could be considered as being essentially non-harmful, the clinical follow up period is still too short to exclude possibility of a later appearance of other unwanted side effects, including tumor formation (Miura et al. 2006, Armesilla-Diaz et al. 2009, Josse et al. 2010, Jeong et al. 2011, Suzuki et al. 2011). For this reason only an autologous cell therapy without extensive manipulations *in vitro* would be considered as a risk devoid and thus recommended for clinical use. Furthermore, optimizing the way of MSCs delivery by more precise transplant location, timing and mode of cell injection would further improve the efficiency of this innovative therapy. In effect, an optimal, tightly controlled system for MSCs isolation and expansion should be designed as a unified standard procedure in neurological clinic.

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