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Review

Mesenchymal stem cells and neuroregeneration in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a prevalent neurodegenerative disorder characterized by a progressive and extensive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) and their terminals in the striatum, which results in debilitating movement disorders. This devastating disease affects over 1 million individuals in the United States and is increasing in incidence worldwide. Currently available pharmacological and surgical therapies ameliorate clinical symptoms in the early stages of disease, but they cannot stop or reverse degeneration of DA neurons. Stem cell therapies have come to the forefront of the PD research field as promising regenerative therapies. The majority of preclinical stem cell studies in experimental models of PD are focused on the idea that stem cell-derived DA neurons could be developed for replacement of diseased neurons. Alternatively, our studies and the studies from other groups suggest that stem cells also have the potential to protect and stimulate regeneration of compromised DA neurons. This review is focused on strategies based on the therapeutic potential for PD of the neurotrophic and neuroregenerative properties of a subclass of stem cells, mesenchymal stem cells (MSCs).

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Introduction

Mesenchymal stem cells (MSCs) were first isolated and defined by Friedenstein and co-workers as plastic-adherent, colony-forming-unit fibroblastic cells (CFU-F) (Friedenstein et al., 1966, 1968, 1970). Later, these cells were named "marrow stromal cells" due to their possible use as a feeder layer for hematopoietic stem cells (Eaves et al., 1991). It has been shown that these cells are multipotent with potential to differentiate into different cells of mesodermal lineage and, since they fulfill the minimal criteria of stem cells in more recent studies, they are now known as "mesenchymal stem cells" or "multipotent mesenchymal stromal cells" (Caplan, 1991; Horwitz et al., 2005; Pittenger et al., 1999). Bone marrow is the primary source of MSCs, but they can also be isolated from various adult and neonatal tissues, such as adipose tissue, peripheral blood, dental pulp, amnion, placenta, umbilical cord and cord blood (Hass et al., 2011; Waddington et al., 2009). It also is easy to procure MSCs from different adult tissues and these cells are more plastic than initially thought since they can transdifferentiate into epithelial, endothelial, and neuronal cells (Brazelton et al., 2000; Dezawa, 2006; Dezawa et al., 2004; Jiang et al., 2002; Spees et al., 2003; Sueblinvong

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et al., 2008; Yue et al., 2008). These characteristics have prompted great interest in the therapeutic potential of MSCs for different diseases, including neurodegenerative disorders such as Parkinson's disease (PD).

PD is a progressive neurodegenerative disease with clinical symptoms of tremor, muscle rigidity, bradykinesia and postural instability. These motor deficits are the consequence of a symptomatic threshold 60% or greater loss of DA-synthesizing neurons in the substantia nigra pars compacta (SNpc) and their terminals in the striatum. Symptoms become more pronounced as the disease progresses due to the continuous degeneration of DA neurons. Existing pharmacological and surgical therapies ameliorate clinical symptoms in the early stages of PD, but as the disease progresses these become less effective and are often accompanied by undesirable side effects of increasing drug doses. None of the available therapies reverse or stop further degeneration of DA neurons pointing to an immense need for a more effective therapy. Diverse therapeutic avenues, such as novel pharmaceuticals targeting DA and other neurotransmitter systems, neurotrophic factors, gene therapies, alteration of ion channels and stem cell approaches, all hold potential for ameliorating the disease process (Bohn, 2000; Chan et al., 2007; Deierborg et al., 2008; Dyson and Barker, 2011; Lindvall and Kokaia, 2009; Parish and Arenas, 2007; Wakeman et al., 2011). Due to the focused loss of DA neurons, PD is particularly suitable for cell and *ex vivo* gene therapy. It has been revealed that stem cells from different sources (Barzilay et al., 2008; Dezawa et al., 2004; Hayase et al., 2009; Kan et al., 2007a; J.H. Kim et al., 2002; Kriks et al., 2011; Nishino et al., 2000; Perrier et al., 2004; Roy et al., 2006; Sakurada et al., 1999; Sanchez-Pernaute et al., 2005; Trzaska et al., 2007; Yang et al., 2004), induced pluripotent stem cells (iPS) (Cai et al., 2010; Chang et al., 2012; Cooper et al., 2010; Ma et al., 2011; Rhee et al., 2011), and even fibroblasts (Caiazzo et al., 2011; Kim et al., 2011; Liu et al., 2012; Pfisterer et al., 2011; Wernig et al., 2008) can give rise to DA neurons under certain culture conditions. Grounded on these findings, cell therapy approaches for PD have been focused mainly on the ability of stem cells to differentiate into DA-producing cells that can replace diseased DA neurons (for reviews, see Ganz et al., 2011; Lindvall and Kokaia, 2009). However, several studies, including studies from our group, have shown that stem cells can protect and/or stimulate regeneration in host-damaged DA neurons (Bouchez et al., 2008; Ebert et al., 2008; Glavaski-Joksimovic et al., 2009, 2010; Park et al., 2008; Shintani et al., 2007; Yasuhara et al., 2006). These studies reveal an alternative strategy for applying stem cell research to PD. Despite the old standing dogma that the adult brain cannot be repaired, regeneration of DA neurons in mature brains in animal models of PD was first revealed following grafting of adrenal medulla tissue into a mouse model of PD (Bohn et al., 1987). This discovery is built on observations of Aguayo and co-workers who showed that neurons in the adult brain had the potential to regrow if provided with a suitable substrate (Ling et al., 2009; Ling and Ecklund, 2011). Other studies in animal PD models bolstered the concept that there is potential for recovery of DA neurons in adult rodent and non-human primate brains as elicited by delivery of growth factor proteins or genes (Bjorklund et al., 1997, 2000; Choi-Lundberg et al., 1997; Gash et al., 1996; Kearns and Gash, 1995; Kordower et al., 2000; Oiwa et al., 2002; Rosenblad et al., 1999), or grafting of primary fetal brain tissue, amnion tissue, or adrenal medulla (Bankiewicz et al., 1990, 1991, 1994; Bohn et al., 1987). Degeneration of DA neurons is also reversible in aged non-human primates following trophic factor gene therapy (Eberling et al., 2009; Kordower et al., 2000). When considered together, the regenerative effects demonstrated in these studies suggest that the degeneration of DA neurons in humans afflicted with PD may also be reversed if a favorable environment is provided. It remains to be proven that diseased human DA neurons will respond similarly to those in animal models of PD. Some positive data from recent clinical trials, albeit variable, suggest that this may be possible (Eberling et al., 2008; Gill et al., 2003; Lang et al., 2006; Marks et al., 2008, 2010; Mittermeyer et al., 2012; Nutt et al., 2003; Patel et al., 2005; Slevin et al., 2005; Venkataramana et al., 2010).

With regard to stem cell approaches for PD, there is a growing body of evidence that naive and genetically modified MSCs can provide a favorable milieu and evoke protection and repair of damaged DA neurons (Blandini et al., 2010; Bouchez et al., 2008; Chao et al., 2009; Cova et al., 2010; Glavaski-Joksimovic et al., 2009, 2010; Park et al., 2008, H.J. Park et al., 2012; Shintani et al., 2007). This review will provide an overview of those studies, and discuss possible mechanisms that underlie MSCs-induced neuroregeneration, as well as the clinical advantages of using this stem cell source.

Potential of MSCs for PD neuroregenerative therapy

MSCs possess several characteristics that make them attractive modalities for use as a novel therapeutic for neurodegenerative disorders, including PD. MSCs can be easily procured and expanded, without the use of other supportive cells. Importantly, MSCs are not burdened with the ethical issues associated with embryonic stem cells and stem cells of a fetal origin. In addition, they are characterized by being able to differentiate along several lineage pathways (Jiang et al., 2002; Nagai et al., 2007; Pittenger et al., 1999). Further, MSCs have been shown in studies of brain injury to migrate to sites of injury (Deng et al., 2011; Hellmann et al., 2006; Ji et al., 2004) and to have immunomodulatory and anti-inflammatory properties (Fibbe et al., 2007; Prockop and Oh, 2012, reviews). Also, unlike stem cells derived from other sources and iPS (Amariglio et al., 2009; Bjorklund et al., 2002; Brederlau et al., 2006; Duinsbergen et al., 2009; Kooreman and Wu, 2010; Morizane and Takahashi, 2012; Roy et al., 2006), MSCs have a low probability of being tumorigenic and a recent open-label phase I study demonstrated the safety of MSCs transplantation into brains of PD patients (Venkataramana et al., 2010). MSCs are also unique compared to other stem cells in that they could theoretically be utilized for personalized medicine in which MSCs for brain engraftment would be collected from the individual to receive grafted cells in order to avoid immune responses and graft rejection (Kan et al., 2007b). These cells are also amenable to genetic modification, which further increases their therapeutic potential (Hodgkinson et al., 2010; Reiser et al., 2005).

Many studies in PD animal models have verified that bone marrow-derived MSCs (BMSCs) have the capacity to protect and regenerate damaged DA neurons (Blandini et al., 2010; Bouchez et al., 2008; Chao et al., 2009; Cova et al., 2010; Danielyan et al., 2011; Li et al., 2001b; Offen et al., 2007; Park et al., 2008; H.J. Park et al., 2012; Pavon-Fuentes et al., 2004; Wang et al., 2010). Li et al. (2001b) were among the first who demonstrated behavioral recovery after BMSCs transplantation in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD. Further, increased viability and migration of transplanted BMSCs were observed after 6-hydroxydopamine (6-OHDA)-induced loss of DA neurons (Hellmann et al., 2006). In addition, BMSCs grafted into the striatum (Blandini et al., 2010; Cova et al., 2010; Pavon-Fuentes et al., 2004), intravenously (Wang et al., 2010) or intranasally (Danielyan et al., 2011) delivered BMSCs were shown to exert neuroprotective effects against nigrostriatal degeneration and to improve motor function in 6-OHDA lesioned rats. Human BMSCs also have a protective effect on the progressive loss of DA neurons induced by carbobenzoxy-L-leucyl-L-leucyl-L-leucinal (MG-132) *in vitro* and *in vivo* in rat (Park et al., 2008). Recent studies (Blandini et al., 2010; Chao et al., 2009; Cova et al., 2010; Danielyan et al., 2011; Kim et al., 2009; Park et al., 2008; H.J. Park et al., 2012) suggest that a number of mechanisms are involved in the regenerative effects of MSCs, as discussed below.

Neurally-induced BMSCs also have been tested for therapeutic effects in PD models by several groups. Ye and co-workers (Ye et al., 2007b) compared the effect of naive BMSCs and BMSCs differentiated into nestin-positive cells transplanted in a 6-OHDA fully lesioned rat PD model. Although both naive and differentiated BMSCs evoked behavioral recovery, the effect of the differentiated cells was more pronounced. However, in studies from Bouchez et al. (Bouchez et al., 2008), BMSCs

grown under standard conditions and BMSCs grown in neuronal differentiation medium were observed to have similar effects on behavioral recovery in a 6-OHDA partially lesioned rat PD model. Offen and colleagues (Offen et al., 2007) also used BMSCs that were induced to adopt neural morphology and express markers of DA neurons, such as tyrosine hydroxylase (TH). When these cells were transplanted in a 6-OHDA mouse model of PD, most of the transplanted cells survived in striatum, expressed TH and behavioral recovery was observed (Offen et al., 2007). A DA-induced subpopulation of human MSCs combined with pharmacologically active microcarriers grafted in a rat PD model also led to protection/repair of the nigrostriatal pathway and behavioral recovery (Delcroix et al., 2011). In addition, micrografted bone marrow derived neuroprogenitor-like cells were shown to induce rejuvenation of host DA neurons in 6-OHDA partially lesioned rat brain (Glavaski-Joksimovic et al., 2009; Fig. 1) and to evoke functional recovery in 6-OHDA fully lesioned rat brain (Dezawa et al., 2004).

MSCs isolated from adipose tissue and umbilical cord have shown beneficial effects in PD models as well. McCoy and co-workers demonstrated that naive and neurally-induced adipose derived MSCs exert neuroprotective effects against 6-OHDA-induced DA neuron death, and they speculate that this was achieved through secretion of trophic factors (McCoy et al., 2008). In addition, MSCs isolated from umbilical cord exhibit neuroprotective and neuroregenerative effects in 6-OHDA (Fu et al., 2006; Mathieu et al., 2012; Weiss et al., 2006) and rotenone lesioned hemiparkinsonian rats (Xiong et al., 2010).

Possible underlying mechanisms in MSCs-evoked repair of DA neurons

Transdifferentiation and fusion as minor factors in MSCs-evoked repair of DA neurons

Although functional recovery following MSCs transplantation has been observed in numerous animal models of neurodegenerative disease, the underlying mechanisms are largely unknown. MSCs isolated from different tissues are quite versatile and can adopt morphological and phenotypic characteristics of neuronal cells under various culture conditions. The majority of the protocols for MSCs neuronal induction utilize different combinations of chemicals, growth factors and signaling molecules (Anghileri et al., 2008; Choong et al., 2007; Chu et al., 2004, 2006; Deng et al., 2001; Fu et al., 2008; B.J. Kim et al., 2002; Long et al., 2005; Suzuki et al., 2004; Tao et al., 2005; Wang et al., 2005; Woodbury et al., 2000). The potential of MSCs to differentiate into neurons also can be enhanced by co-culture with glial, neuronal, and neuronal stem cells (Alexanian, 2005; Alexanian et al., 2008; Jiang et al., 2002, 2003; Sanchez-Ramos et al., 2000; Wislet-Gendebien et al., 2003, 2005a), or by astrocyte or neuronal conditioned medium (Joannides et al., 2003; Rivera et al., 2006). In addition, MSCs neural transdifferentiation can be boosted by over-expression of certain genes such as noggin (Kohyama et al., 2001), notch intracellular domain (*NICD*) (Dezawa et al., 2004; Fig. 2), and brain-derived neurotrophic factor (*BDNF*) (Zhao et al., 2004), genes that are important for neural development and function. Similarly, MSCs differentiation into DA neurons can be achieved through different protocols based on chemical induction, gene transfection, co-culturing and use of conditioned medium (Barzilay et al., 2009; Datta et al., 2011; Dezawa et al., 2004; Fu et al., 2006; Guo et al., 2005; Hermann et al., 2004; Jiang et al., 2003; Kan et al., 2007a; Pacary et al., 2006; Trzaska et al., 2009; Zhang et al., 2008). However, the transdifferentiation potential of MSCs to neurons, while intriguing, remains controversial and needs further evaluation. A few studies have raised doubts regarding ability of MSCs to transdifferentiate into neurons, suggesting instead that MSCs exposed to chemical induction adopt neuronal-like morphology and express various neural specific markers due to cellular toxicity, cell shrinkage and cytoskeletal alterations (Bertani et al., 2005; Lu et al., 2004; Neuhuber et al., 2004). Moreover, naive MSCs have been reported to express the neuroprogenitor marker nestin (Tondreau et al., 2004;

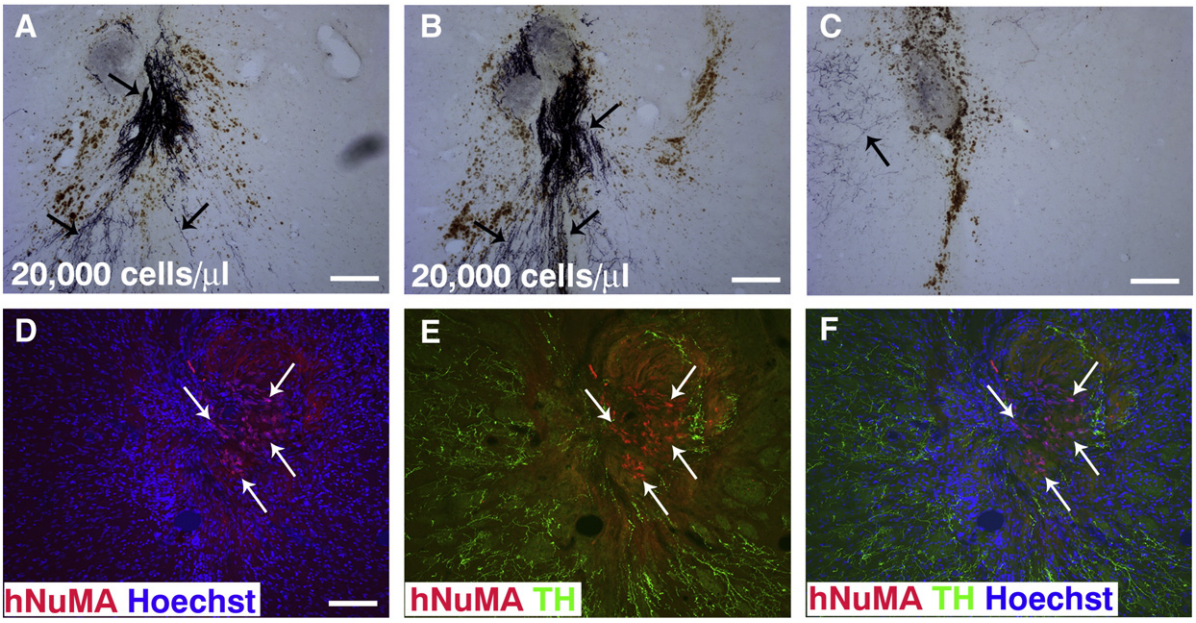

Fig. 1. Effect of human Notch-induced BMSCs (SB623 cells) grafts on recovery of DA fibers in the Fisher 344 rat striatum lesioned with the neurotoxin 6-OHDA. Cells were grafted 1 week after the lesion and rats were euthanized at 4 weeks. A–B, sections stained for TH-IR using a nickel-enhanced diaminobenzidine method (black). Note dense TH-IR fibers (arrows) around SB623 graft sites in two different rats that received SB623 cells in a concentration of 20,000 cells/μl one week after lesioning with 6-OHDA. C, in vehicle injected control rats, only sparse TH-IR fibers were present around the injection site (arrow). In panels A through C, brown cells show macrophages or dead cells in the needle track. D–F, recovery of host DA fibers around grafted SB623 cells as visualized by hNuMA-IR and TH-IR. D, overlay of hNuMA (red) and Hoechst nuclear staining (blue) showing surviving SB623 cells (marked with arrows) that co-express hNuMA (red) and Hoechst nuclear (blue) staining at 3 weeks in the striatum of a rat that received SB623 cells in a concentration of 20,000 cells/μl one week after lesioning with 6-OHDA. E, overlay of hNuMA-IR (red) and TH-IR (green) in the same section shown on panel D. Note recovery of TH-IR fibers surrounding the SB623 cell graft, but no overlap of hNuMA-IR with TH-IR, implying a host origin of the TH-IR fibers. F, overlay of the hNuMA-IR (red), Hoechst (blue) and TH-IR (green) in the same section. Bars in A–F = 100 μm.
Panels are reproduced from Glavaski-Joksimovic A. et al., Cell Transplant 18 (2009) 801–814, with the permission of Cognizant Communication Corporation.

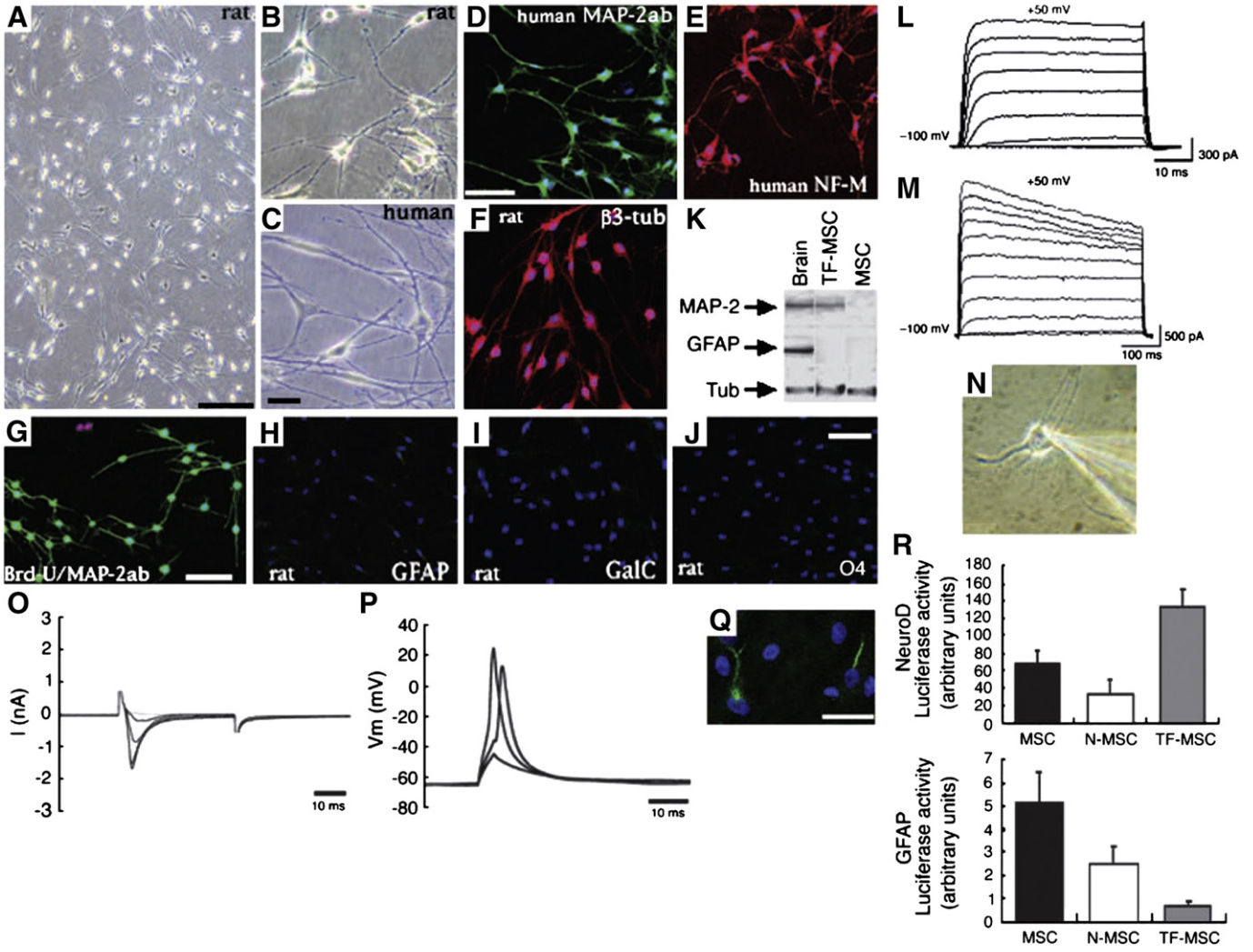

Fig. 2. Analysis of TF-MSCs (5 days after trophic factor induction). A–C, phase contrast of TF-MSCs from rats (A and B) and humans (C). Bars in A = 200 μm, and B and C = 50 μm. D–F and H–J, immunocytochemical analysis of neuronal and glial markers in rat (F, and H–J) and human (D and E) TF-MSCs. MAP-2ab (D), neurofilament-M (E), and β-tubulin isotype 3 (F) were detected. None of the cells were reactive to GFAP (H), GalC (I), and O4 (J). G, the Brd-U labeling of rat TF-MSCs. MAP-2ab-positive cells (green) did not incorporate BrdU (red), whereas negative cells were occasionally incorporated with BrdU. Bars in D–J = 100 μm. K, Western blot analysis of MAP-2ab and GFAP rat samples. Brain, positive control; TF-MSCs. β-tubulin (tub) as a loading control. L–Q, patch clamp. K + current increased with trophic factor induction up to approximately 1600 pA and 4000 pA in rat (L) and human (M) TF-MSCs, respectively. N, phase contrast of human TF-MSCs recorded in (M). O, voltage-gated inward current recorded in rat BDNF + NGF-treated TF-MSCs. A series of Na current to show the process of block by TTX. Capacity current was blanked. P, action potentials from rat BDNF + NGF-treated TF-MSCs; subthreshold, threshold, and suprathreshold current injections were made. Q, immunocytochemistry of sodium channel (green). Bar = 30 μm. R, relative promoter activities of NeuroD and GFAP in rat MSCs, N-MSCs, and TF-MSCs.
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Wislet-Gendebien et al., 2003, 2005b), as well as a variety of neuronal genes and proteins, including markers for DA neurons (Arnhold et al., 2006; Blondheim et al., 2006; Deng et al., 2006; Kramer et al., 2006; Montzka et al., 2009; Tondreau et al., 2004; Woodbury et al., 2002; Zhang and Alexanian, 2012), which further complicate the evaluation of MSCs to transdifferentiate. However, observations of cytokine-induced MSCs morphological and phenotypic changes by time-lapse microscopy suggest that these result from active and dynamic cellular processes, not simply from culture artifacts (Tao et al., 2005). The ability of MSCs to transdifferentiate into functional neurons is further bolstered by demonstrations that neurally-induced MSCs express calcium, potassium and sodium channels, can generate action potentials, and support synaptic transmission (Cho et al., 2005; Dezawa et al., 2004; Fox et al., 2010; Jang et al., 2010; Mareschi et al., 2006; H.W. Park et al., 2012; Preston et al., 1996; Tondreau et al., 2008; Wislet-Gendebien et al., 2005a; Zeng et al., 2011). Several *in vivo* studies also demonstrated the capacity of MSCs to differentiate into neuronal cells following grafting, but the number of observed MSCs-derived neurons and glial cells was rather small and did not restore a normal tissue cytoarchitecture (Alexanian et al., 2008; Chen et al., 2001; Dezawa et al., 2004; Kopen et al., 1999; Li et al., 2001a; Lu et al., 2006; Mezey et al., 2003; Mimura et al., 2005; Park et al., 2008; Zhao et al., 2002). It remains uncertain whether MSCs-derived neurons can form synaptic connections with host cells or be properly incorporated into host neuronal circuitries. It also has been suggested that grafted MSCs fuse with host cells, including neurons (Alvarez-Dolado et al., 2003; Terada et al., 2002; Vassilopoulos et al., 2003; Wang et al., 2003), although this appears to be a very a rare phenomenon (Colletti et al., 2009; Lopez-Iglesias et al., 2011; Terada et al., 2002). In summary, it is unlikely that either transdifferentiation or fusion of MSCs with host neurons is a major factor contributing to MSCs-induced functional recovery. Rather, the experimental data imply that the neurological improvement observed after MSCs transplantation into the injured or ischemic brain is achieved through MSCs secretion of growth factors and cytokines that create a favorable environment for regeneration and facilitate intrinsic restorative processes (Kim et al., 2010; Li and Chopp, 2009; Li et al., 2002; Parr et al., 2007; Pisati et al., 2007). Similarly, several studies suggested that neuroprotective and restorative effects of MSCs in PD animal

models (Fig. 3.) are achieved mainly through secretion of growth factors and cytokines, enhancing endogenous restorative processes, immunomodulatory and anti-inflammatory effects (Blandini et al., 2010; Bouchez et al., 2008; Chao et al., 2009; Cova et al., 2010; Kim et al., 2009; Park et al., 2008; H.J. Park et al., 2012; Shintani et al., 2007).

MSCs paracrine factors and DA neuron protection and repair

MSCs have been reported to secrete an array of growth factors and cytokines, including BDNF, nerve growth factor (NGF), glial-cell-line-derived neurotrophic factor (GDNF), fibroblast growth factor 2 and 8 (FGF2 and FGF8), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), ciliary neuronotrophic factor (CNTF), insulin-like growth factor 1 (IGF-1), neurotrophin-3 (NT-3) and stromal cell-derived factor-1 (SDF-1) (Arnhold et al., 2006; Bouchez et al., 2008; Chen et al., 2002; Crigler et al., 2006; Croitoru-Lamoury et al., 2007; Honczarenko et al., 2006; Jiang et al., 2010; Lattanzi et al., 2011; Li et al., 2002; Pisati et al., 2007; Shintani et al., 2007; Tate et al., 2010; Wakabayashi et al., 2010; Wilkins et al., 2009). MSCs also express neurotrophin low-affinity nerve growth factor receptors (NGFRs) and high-affinity tyrosine kinase (trk) receptors and can respond to neuronal tissue environment with both neurotrophin protein release and neurotrophin receptor expression (Labouyrie et al., 1999; Pisati et al., 2007). Some growth factors secreted from MSCs, including GDNF, BDNF, bFGF, and CNTF, elicit neurotrophic and neuroprotective effects on DA neurons (Chadi et al., 1993; Choi-Lundberg et al., 1997; Engele and Bohn, 1991; Ferrari et al., 1989; Hagg and Varon, 1993; Hyman et al., 1991; Kearns and Gash, 1995; Lin et al., 1993; Magal et al., 1993; Sauer et al., 1993). Further, it has been shown that following grafting into parkinsonian rat brains, MSCs differentiate into glial cells that can release different neurotrophic factors protecting against the neurotoxin, 6-OHDA (Blandini et al., 2010). In the same study, increased expression of GDNF was observed in the SNpc of grafted rats, and authors speculated that glial differentiation of MSCs particularly reinforced GDNF secretion, which led to the DA neuroprotection (Blandini et al., 2010). Studies in which human MSCs were grafted into a mouse or rat brain respectively, demonstrated that grafted MSCs can also stimulate expression of endogenous neurotrophic factors as demonstrated by immunostaining and ELISAs for mouse neurotrophins (Munoz et al., 2005), or by quantitative real-time RT-PCR and Western blot analysis for rat neurotrophins (Wakabayashi et al., 2010). In addition, transplantation of undifferentiated and neuronal-primed MSCs into lesioned rat striatum can evoke an inflammatory response, which involves activation of host microglia/macrophages and astrocytes (Khoo et al., 2011). These activated glial cells may produce trophic factors, such as BDNF, GDNF, NGF, NT-3, interleukin-1ß and CNTF, that stimulate DA neuronal regeneration (Asada et al., 1995; Batchelor et al., 1999; Chen et al., 2006; Ho and Blum, 1997; Schaar et al., 1993; Wang et al., 1994). Thus, it is presumable that growth factors secreted from grafted MSCs and stimulated host cells are implicated in the therapeutic effects of MSCs in different animal models of PD. In this regard, it has been shown that MSCs-secreted growth factors up-regulate TH gene expression and DA content in rat embryonic ventral mesencephalic cells *in vitro* (Jin et al., 2008). Similarly, Shintani and co-workers have shown that MSCs derived-conditioned medium (MSCs-CM) significantly decreases the DA neuronal death after serum deprivation or exposure to the neurotoxin 6-OHDA (Shintani et al., 2007). In addition, pretreatment of embryonic DA neurons with MSCs-CM increases their survival after grafting in a rat model of PD, implying that MSCs secrete diffusible factors that promote survival of DA neurons (Shintani et al., 2007). Also, the ability of MSCs to induce survival and neurite outgrowth in the SH-SY5Y neuroblastoma cell line has been shown to correlate with the level of BDNF and to be partially inhibited by a BDNF antibody (Crigler et al., 2006). *In vivo*, studies also suggest the involvement of growth factors in the observed increases in DA levels and TH immunoreactivity, and in the recovery from motor deficits in PD animal models after MSCs transplantation (Bouchez et al., 2008; Park et al., 2008). In addition, a prominent recovery of DA function was observed after transplantation of MSCs that were directed *in vitro* toward neurotrophic factor-secreting cells (Bahat-Stroomza et al., 2009; Sadan et al., 2009;

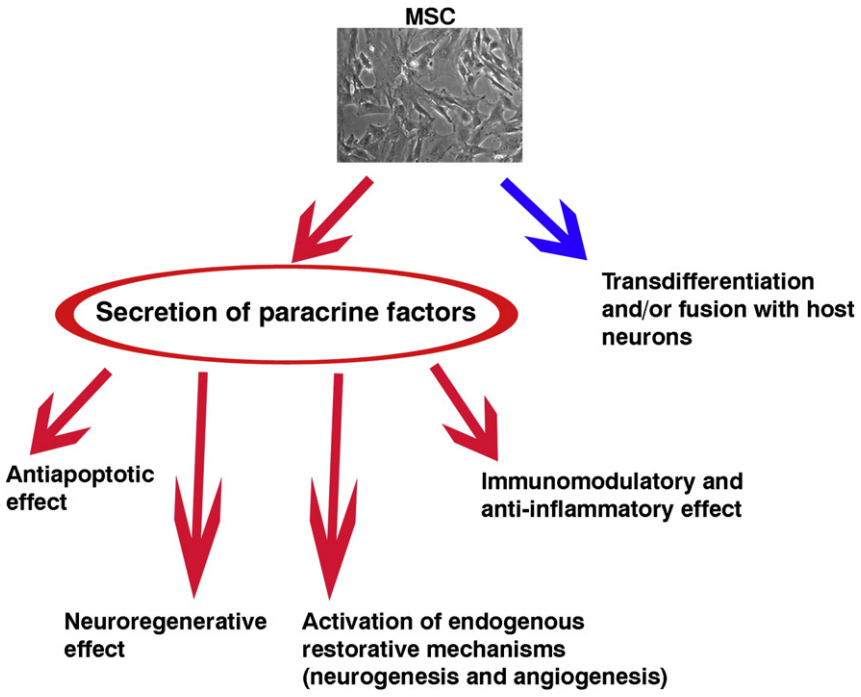
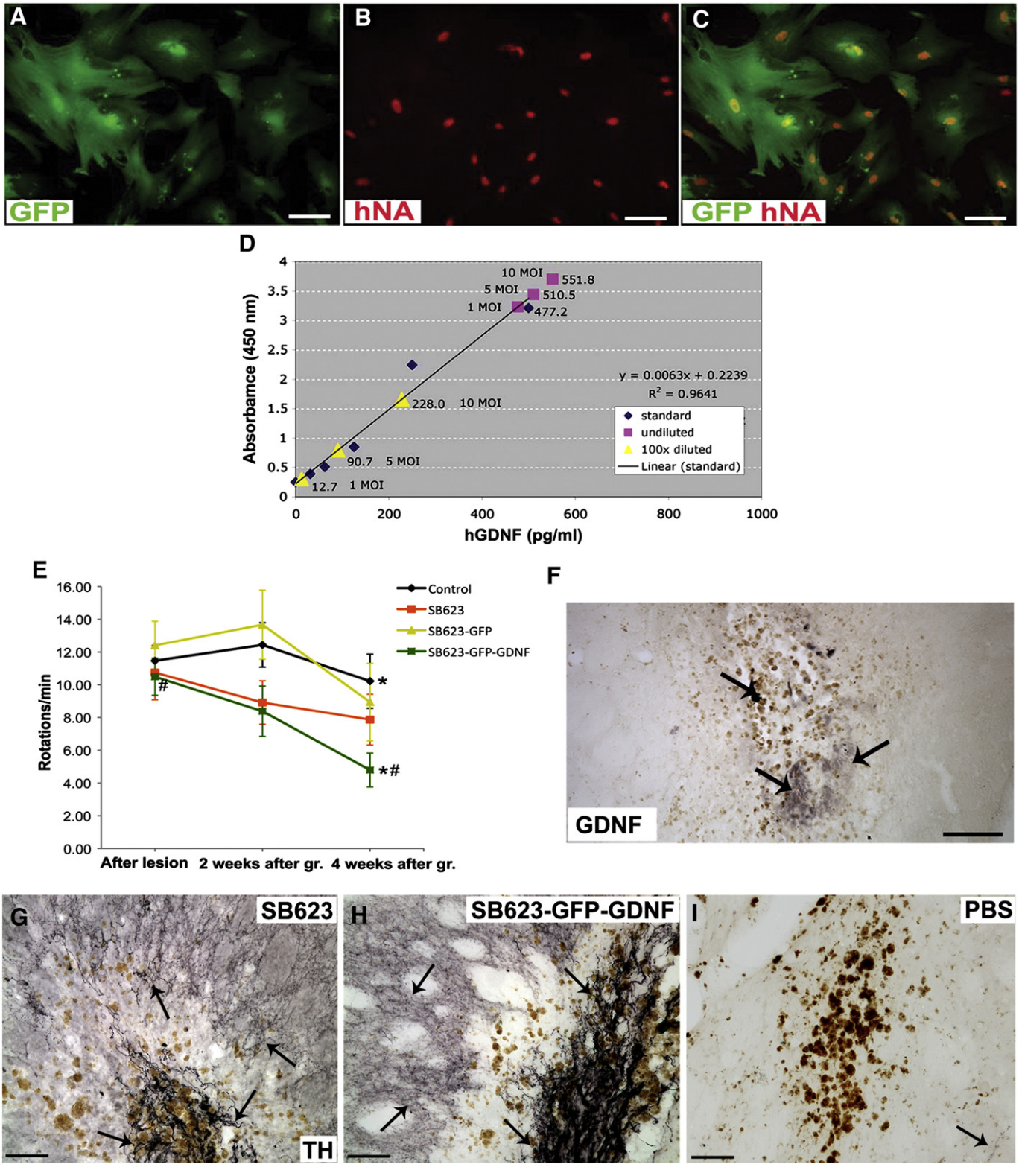


Fig. 3. Schematic representation of possible mechanisms that are involved in MSCs therapeutic effects for PD. MSCs can protect and/or stimulate regeneration in host-damaged DA neurons, mainly through secretion of different growth factors, cytokines, extracellular matrix proteins (ECM), and neuro-regulatory molecules that have the capacity to decrease loss of DA neurons (antiapoptotic effect) and create a favorable environment for neuronal regeneration. Through release of paracrine factors, MSCs are also able to affect the host tissue and facilitate intrinsic restorative processes such as neurogenesis and angiogenesis. Immunomodulatory and anti-inflammatory properties of MSCs are also implicated in their ability to protect and repair DA neurons. Compared to paracrine effects, capacity of MSCs to transdifferentiate into neurons and/or fuse with the host neurons is in less extent involved in their beneficial effects for PD.

Somoza et al., 2010). In our studies with Notch-induced human MSCs in a rat model of PD, we observed rejuvenation of host DA neurons although long term survival of grafted cells was very limited, further suggesting that grafted cells initially secrete trophic factors and evoke endogenous restorative mechanisms (Glavaski-Joksimovic et al., 2009). Since the grafted cells did not survive, there are two possible explanations for the observed increases in host TH-immunoreactive (IR) fibers in striatum following grafting of naive, neurally-induced and Notch-induced MSCs (Bouchez et al., 2008; Glavaski-Joksimovic et al., 2009; Park et al., 2008), either an up-regulation of TH expression in existing host fibers or de novo fiber growth from host DA neurons. It is also feasible that grafted MSCs decrease DA neuronal loss through their anti-apoptotic effects. In this respect, a decrease in apoptotic markers and an increase in neuronal survival have been demonstrated following MSCs transplantation in ischemic and injured brains (Kim et al., 2010; Li et al., 2002, 2010). Moreover, in rats treated with MG-132,



a proteasome inhibitor that causes progressive loss of DA neurons, administration of human MSCs significantly ameliorates the declines in TH-IR cells and caspase-3 activity (Park et al., 2008). In addition, a recent study from Wang and co-workers demonstrated that the neuroprotective effect of MSCs on 6-OHDA exposed DA neurons is at least in part mediated through an anti-apoptotic action of SDF-1 (Wang et al., 2010). It also has been suggested that MSCs anti-apoptotic effects could be achieved through secretion of VEGF, HGF and BDNF, all of which increase the levels of the pro-survival factor Akt (Lu et al., 2011).

Besides growth factors, MSCs express various cytokines and potent neuro-regulatory molecules that also are known to promote neuronal survival and regeneration (Crigler et al., 2006; Tate et al., 2010). MSCs also produce extracellular matrix proteins (ECM) that can support neural cell attachment, growth, neuritogenesis and functional restoration (Aizman et al., 2009; Lai et al., 2010; Zhao et al., 2002). Notch-induced MSCs also express ECM (Aizman et al., 2009) and this might be implicated in the rejuvenation of host DA neurons observed in our studies in 6-OHDA partially lesioned PD rat model (Glavaski-Joksimovic et al., 2009).

MSCs and DA neuron repair through interaction with host cells. In addition to their effects on host DA neurons, grafted MSCs have been shown to affect endogenous neural stem cells (NSCs), glial cells and blood vessels through release of paracrine factors, which further contributes to the neuronal tissue repair and functional recovery.

In vitro studies have shown that MSCs provide signals that promote NSCs neuronal and glial differentiation (Bai et al., 2007; Robinson et al., 2011). In a particularly interesting study, Munoz and co-workers observed that transplantation of human MSCs into mouse hippocampus stimulated proliferation, migration and differentiation of the endogenous NSCs (Munoz et al., 2005). More recent studies also demonstrated increased neurogenesis after intrahippocampal and intracerebroventricular MSCs transplantation (Coquery et al., 2012; Tfilin et al., 2010). It is proposed that MSCs affect endogenous NSCs through increase in expression of NGF, VEGF, CNTF, FGF-2 and the polycomb family transcriptional repressor BMI-1 in the hippocampus (Munoz et al., 2005). Another possibility is that MSCs affect endogenous NSCs indirectly through stimulation of astrocytes to secrete growth factors, such as BDNF and NGF, which increase neurogenesis (Li et al., 2002; Munoz et al., 2005; Song et al., 2002). Studies of Kan and colleagues reveal that transplantation of human MSCs into the subventricular zone (SVZ) of intact mice housed in an enriched environment stimulates the proliferation and maturation of endogenous progenitors toward the neuronal phenotype (Kan et al., 2011). In addition, it has been shown that intracerebral MSCs administration and intravenous MSCs administration increase proliferation and differentiation of endogenous NSCs after stroke and traumatic brain injury (Bao et al., 2011; Li et al., 2002, 2010; Mahmood et al., 2004; Pavlichenko et al., 2008). Recent studies reveal that MSCs have similar effects on endogenous NSCs in animal models of PD (Cova et al., 2010; H.J. Park et al., 2012). Cova and co-workers showed that transplantation of human MSCs in 6-OHDA lesioned rat striatum increases neurogenesis in SVZ, while SVZ astrogenesis was not observed (Cova et al., 2010). They proposed that reciprocal influences between grafted MSCs and endogenous NSCs are important for the observed rescue of DA neurons (Cova et al., 2010). In addition, studies from Park et al. show that transplantation of human MSCs in an MPTP mouse model of PD augments neurogenesis both in SVZ and SN and increases differentiation of NSCs toward DA neurons (H.J. Park et al., 2012). These authors suggest that the effects of grafted MSCs on endogenous NSCs could be achieved through EGF secretion and an increased expression of EGF receptor in the SVZ (H.J. Park et al., 2012).

A significant feature of the regenerative effects of MSCs is their ability to promote endothelial cell proliferation and angiogenesis (Kaigler et al., 2003; Kinnaird et al., 2004a). The MSC's effect on blood vessels may be mediated through angiogenic factors, such as VEGF, FGF, HGF, SDF-1, angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2) and matrix metalloproteinase-1 (MMP-1) (Burdon et al., 2011; Kinnaird et al., 2004a, 2004b; Tate et al., 2010). The formation of new blood vessels following MSCs transplantation might be associated with the MSCs neuroregenerative effect since angiogenesis and neurogenesis are coupled processes (Palmer et al., 2000; Teng et al., 2008). Supporting this particular point are studies showing an increase in angiogenesis associated with neurological recovery following MSCs grafting in animal models of stroke (Omori et al., 2008; Onda et al., 2008; Pavlichenko et al., 2008) and traumatic brain injury (TBI) (Xiong et al., 2009). Recovery of a compromised blood brain barrier (BBB) also was reported following intravenous administration of MSCs in an MPTP mouse model of PD, suggesting that this is another mechanism involved in protection of DA neurons (Chao et al., 2009). Further, in our studies, we have observed dense GLUT-1-IR blood vessels around grafted Notch-induced MSCs and have speculated that an effect of MSCs on blood vessels was involved in the observed rejuvenation of DA neurons (Glavaski-Joksimovic et al., 2009). Most likely this effect was mediated through VEGF and/or other angiogenic factors that are secreted from Notch-induced MSCs (Tate et al., 2010).

Immunomodulatory and anti-inflammatory effects of MSCs in animal models of PD

There is increasing body of evidence that inflammation and microglia proliferation are implicated in the pathogenesis of PD, (Tansey and Goldberg, 2010, review). Extensive proliferation of activated microglia has been observed postmortem in SN of PD patients (Langston et al., 1999; McGeer et al., 1988). Activated microglia are also present in patients with early PD and they are correlated with the degree of DA neuronal loss (Ouchi et al., 2005). Moreover, elevated levels of proinflammatory cytokines, such as tumor necrosis factor (TNF), interleukin-1 beta (IL-1β) and interferon-gamma (IFN-γ) have been detected in brains of PD patients (Boka et al., 1994; Hunot et al., 1999; Mogi et al., 1994; Nagatsu et al., 2000). Reactive microglia and proinflammatory cytokines are also expressed in different animal models of PD (Cicchetti et al., 2002; Depino et al., 2003; Gao et al., 2002) and degeneration of DA neurons caused by lipopolysaccharide (LPS) or MPTP can be prevented by administration of anti-inflammatory drugs, such as aspirin, salicylate, dexamethasone and the selective COX-2 inhibitor rofecoxib (Aubin et al., 1998; Castano et al., 2002; Teismann et al., 2003). There is also evidence

Fig. 4. Effect of non-transduced and GDNF and/or hrGFP transduced SB623 cell grafts on recovery of DA fibers in the Fisher 344 rat striatum lesioned with 6-OHDA. 72 h after lentiviral transduction more than 95% of SB623 cells express GFP (green) (A). In addition cells were stained with anti-human nuclear antigen (hNA; red) antibody (B). C, overlaid A and B images. Note that almost all cells display green GFP fluorescence and red hNA staining. D, 72 h after transduction SB623 cells (yellow + pink) secrete a significant amount of GDNF into the culture medium as determined by ELISA. Undiluted medium samples (pink squares) from cells infected at 1, 5 or 10 MOI and corresponding samples diluted 100-fold (yellow triangles) to be in the linear range of standards (blue diamonds). E, GDNF and/or hrGFP transduced SB623 cells were grafted 1 week after the lesion and rats were euthanized at 5 weeks post-grafting. The majority of rats that received GDNF transduced SB623 cells had significantly fewer amphetamine induced rotations at 4 weeks post-grafting compared to post lesion rotations (#; $p < 0.01$) and compared to control rats (*; $p < 0.03$). F, expression of GDNF in rat striatum at 5 weeks post-grafting of GDNF secreting SB623 cells was observed using nickel-enhanced DAB staining (black). GDNF-IR (arrows) observed in the graft site of a rat that received GDNF transduced SB623 cells. G–I, sections stained for TH-IR using nickel-enhanced DAB staining (black). Note dense TH-IR fibers (arrows) in graft sites in rat that received non-transduced SB623 cells in G, and even denser TH-IR fibers in a rat that received GFP-GDNF transduced SB623 cells in H. I, in vehicle injected control rats, only sparse TH-IR fibers (arrow) were observed around the injection. In panels F and G through I, brown cells represent macrophages or dead grafted cells in the needle track. Bars in A–C and G–I = 50 μm and F = 100 μm.
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that nonsteroidal anti-inflammatory drugs have a protective role in PD patients, as well (Chen et al., 2003; Wahner et al., 2007). In addition, it has been shown that immunosuppressant cyclosporin A attenuates DA degeneration in PD animal models (Kitamura et al., 1994; Matsuura et al., 1996, 1997a, 1997b). The involvement of inflammation in PD pathophysiology suggests that immunomodulatory and anti-inflammatory effects of MSCs may partially underlie their beneficial effects after transplantation in animal models of PD. Numerous pieces of evidence suggest that MSCs have a dual role in the immune system and that they either can suppress or activate an immune response (Stagg, 2007). It has been reported that transplantation of allogeneic MSCs into a rat model of PD can evoke a cellular immune response (Camp et al., 2009). On the other hand, MSCs can elicit a suppressive effect on a broad range of immune cells, including T lymphocytes, B lymphocytes, dendritic cells and natural killer (NK) cells (Mezey et al., 2010; Nauta and Fibbe, 2007; Stagg, 2007). This interaction with the immune cells is achieved through cell–cell contact and release of different factors that have immunomodulatory effects (Nauta and Fibbe, 2007). Some of MSCs released factors that are suggested to be implicated in immunomodulation include interleukin-6 (IL-6), transforming growth factor beta (TGFβ), prostaglandin E2 (PGE2), HGF, indoleamine 2,3-dioxygenase (IDO) and monocyte colony stimulating factor (M-CSF) (Mezey et al., 2010; Nauta and Fibbe, 2007). Conversely, MSCs can decrease inflammatory responses through various mechanisms. Some of MSCs anti-inflammatory actions are achieved through: a) expression of IL-1 receptor antagonist, b) secretion of anti-TNFα stimulated gene/protein 6 (TSG-6) which modulates the cascade of proinflammatory cytokines from resident macrophages, c) release of PGE2 which converts macrophages to a phenotype that secretes IL-10, and d) expression of stanniocalcin-1 that reduces reactive oxygen species (Bartosh et al., 2010; Lee et al., 2009; Matysiak et al., 2011; Nemeth et al., 2009; Oh et al., 2012; Ortiz et al., 2007; Prockop and Oh, 2012; Roddy et al., 2011). It has been shown that MSCs exert therapeutic effects through immunomodulatory and anti-inflammatory actions in autoimmune encephalomyelitis and TBI (Galindo et al., 2011; Gerdoni et al., 2007; Zappia et al., 2005). Recent studies also reveal similar MSCs effects in PD. For example, Kim and co-workers demonstrated that MSCs have the ability to protect DA neurons through anti-inflammatory actions that include decreased LPS-induced microglia activation and production of nitric oxide and TNFα (Kim et al., 2009). Similarly, Chao et al. (2009) revealed that the BBB is compromised in an MPTP mouse PD model and observed infiltration of a peripheral inflammatory molecule mannose-binding lectin (MBL) in the brain, thus suggesting involvement of peripheral immune components in the pathogenesis of PD. Further, their studies have shown that intravenous administration of mouse BMSCs protects DA neurons from MPTP toxicity through repair of BBB integrity, reduced levels of MBL in the brain and decreased microglial activation (Chao et al., 2009). Together these studies illustrate the importance of MSCs immunomodulatory and anti-inflammatory effects in developing treatments for PD.

Genetically modified MSCs and their therapeutic potential in PD

The beneficial effects of MSCs for PD can be enhanced by their genetic modification to overexpress therapeutic genes. Numerous studies have demonstrated that protein or gene delivery of growth factors, particularly GDNF and neurturin, effectively protects DA neurons in an array of rodent and primate models of PD (Bjorklund et al., 2000; Choi-Lundberg et al., 1997, 1998; Connor et al., 1999; Eberling et al., 2009; Gash et al., 1996; Gasmi et al., 2007; Herzog et al., 2007; Hoffer et al., 1994; Johnston et al., 2009; Kells et al., 2010; Kordower et al., 2000, 2006; Kozlowski et al., 2000; Natsume et al., 2001; Oiwa et al., 2002; Rosenblad et al., 1999; Tomac et al., 1995). Ex vivo growth factor gene transfer into various somatic cells and stem cells/progenitors followed by transplantation into the parkinsonian brains, has also been investigated as an alternative delivery approach (Cunningham et al., 1991; Date et al., 1996, 1997; Ebert et al., 2008; Emborg et al., 2008; Frim et al., 1994; Galpern et al., 1996; Grandoso et al., 2007; Lindvall and Wahlberg, 2008; Liu et al., 2007; McLay et al., 2001; Schumacher et al., 1991; Wilby et al., 1999; Yasuhara et al., 2004, 2005; Yoshimoto et al., 1995; Zhang et al., 2001).

MSCs are a prime candidate for ex vivo growth factor gene delivery due to their amenability for genetic modification and advantages for clinical applications, as discussed above. Several groups have investigated the potential of MSCs genetically engineered with GDNF, either by transfection or viral transduction, to deliver this potent neurotrophic factor for DA neurons in the brain. Park and co-workers first demonstrated that MSCs are a suitable vehicle for delivering GDNF into the parkinsonian mouse brain (Park et al., 2001). In their study, MPTP mice that were intravenously injected with GDNF-engineered BMSCs possessed more TH-IR neurons and fibers and demonstrated more prominent behavioral recovery compared to control mice that received unmodified BMSCs (Park et al., 2001). In a lactacystin-induced PD rat model, intrastriatal transplantation of naive or GDNF-engineered BMSCs significantly rescued DA neurons and evoked behavioral recovery, but rats that received the GDNF-engineered MSCs showed significantly greater recovery (Wu et al., 2010). Moloney and colleagues (Moloney et al., 2010) studied the effect of naive and GDNF-transduced MSCs transplanted into rat striatum four days prior to a 6-OHDA-induced lesion of DA neurons. Although behavioral recovery was not observed in either experimental group, transplantation of GDNF-transduced cells evoked sprouting of TH-IR fibers in the immediate vicinity of the transplants, suggesting a localized GDNF trophic effect (Moloney et al., 2010). Similarly, we observed an increased density of TH-IR fibers around the grafted Notch induced-BMSCs (SB623 cells; SanBio Inc.) and Notch-induced BMSCs transduced with GDNFs that were grafted into the striatum of 6-OHDA partially lesioned rats (Glavaski-Joksimovic et al., 2010). However, the observed effect on host TH-IR fibers was more prominent in rats that were grafted with the GDNF transduced cells, and this correlated with behavioral recovery only in this experimental group (Glavaski-Joksimovic et al., 2010; Fig. 4). Shi and colleagues (Shi et al., 2011) studied the effects of BMSCs that were transduced with TH and GDNF in 6-OHDA lesioned rats. In their study, naive BMSCs did not affect apomorphine-induced rotational behavior, while the average rotational rates were significantly decreased in rats grafted with TH- and GDNF-modified BMSCs (Shi et al., 2011). Transplantation of neurturin- or NGF-modified BMSCs in PD rats also had more prominent effects on behavioral recovery than transplantation of unmodified BMSCs (Wang et al., 2008; Ye et al., 2007a). Further, VEGF over-expression in human umbilical cord MSCs significantly increased DA differentiation of these cells and enhanced their therapeutic effectiveness in a rotenone-induced rat PD model (Xiong et al., 2011). In addition to MSCs modified with growth factors, TH-engineered BMSCs (Lu et al., 2005) and BMSCs transduced to produce L-3,4-dihydroxyphenylalanine (L-DOPA) (Schwarz et al., 1999) were shown to have significant therapeutic effects in PD rats. Together these studies suggest that MSCs could be developed as a valuable gene delivery vehicle for PD gene therapy.

Conclusion

There are numerous reasons for optimism concerning the use of MSCs for neural repair and protection in PD therapy. The main body of evidence on the effects of MSCs grafted into animal models of PD suggests that MSCs act through paracrine mechanisms, release of various neurotrophic, anti-inflammatory, immunomodulatory, anti-apoptotic and angiogenic factors to affect cells in the host brain tissue and promote recovery of compromised DA neurons. There is little support for the hypothesis that MSCs promote recovery in animal models of PD through replacement of DA neurons. In the future, it will be necessary to conduct well-designed and carefully controlled clinical trials to verify these regenerative effects of MSCs in non-human primates, and then potentially in clinical trials to determine if the regenerative effects observed in animal models will be applicable to diseased DA neurons.

Although the MSCs approach is early in the clinical pipeline, the findings to date suggest this as a promising novel approach for PD.

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