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Concise Review: Adult Mesenchymal Stem Cells, Adult Neural Crest Stem Cells, and Therapy of Neurological Pathologies: A State of Play

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ABSTRACT

Adult stem cells are endowed with in vitro multilineage differentiation abilities and constitute an attractive autologous source of material for cell therapy in neurological disorders. With regard to lately published results, the ability of adult mesenchymal stem cells (MSCs) and neural crest stem cells (NCSCs) to integrate and differentiate into neurons once inside the central nervous system (CNS) is currently questioned. For this review, we collected exhaustive data on MSC/NCSC neural differentiation in vitro. We then analyzed preclinical cell therapy experiments in different models for neurological diseases and concluded that neural differentiation is probably not the leading property of adult MSCs and NCSCs concerning neurological pathology management. A fine analysis of the molecules that are secreted by MSCs and NCSCs would definitely be of significant interest regarding their important contribution to the clinical and pathological recovery after CNS lesions. STEM CELLS TRANSLATIONAL MEDICINE *2013;2:000–000*

INTRODUCTION

Neurodegenerative and acute neurological pathologies represent a critical issue in clinical research, since no complete recovery of the central nervous system (CNS) functionality can be achieved in a lot of situations with current therapeutic means (despite symptomatic enhancements). In adults, whereas restricted brain areas still house cells competent to generate newborn neurons [1], this limited neurogenesis does not seem to be sufficient to enable neuronal regeneration in cases of traumatic, ischemic, or degenerative damages of the CNS. Therefore, other strategies have to be considered in order to restore the injured system, and stem cell-based replacement therapies have already been proposed and studied worldwide in a perspective of neurological disease management.

Stem cells are characterized as cells endowed with continuous self-renewal ability and pluri- or multipotentiality and could consequently give rise to a large panel of cell types [2]. Nongerminal stem cells are classified into different categories: (a) Embryonic stem (ES) cells are found in the inner cell mass of blastocyst and are pluripotent stem cells that can generate any mature cell of each of the three germ layers [3]; (b) induced pluripotent stem (iPS) are adult somatic cells that are reprogrammed into pluripotent cells with ES-like abilities [4, 5]; and (c) somatic stem cells (also named adult stem cells although already present in the embryo) are tissue-specific and more restricted than ES cells in terms of differentiation capabilities. They can be isolated from various fetal and adult tissues, which make them an attractive supply of material for cell therapy. The use of adult somatic stem cells definitely remains of significant interest regarding technical, ethical, and immunological issues concerning cell transplantation for brain diseases. In this regard, mesenchymal stem cells (MSCs) and neural crest stem cells (NCSCs) that can be found in various locations of the adult organism (and even in perinatal tissues) represent an important source of easily accessible multipotent cells to use in a cell therapy capacity [6].

ADULT MESENCHYMAL AND NEURAL CREST STEM CELLS

MSCs are plastic-adherent, fibroblast-like cells, which are typically able to self-renew and differentiate into tissues that arise from the mesodermic lineage, such as bone, fat, and cartilage. Whereas those cells have traditionally been isolated from bone marrow stroma (bone marrow stromal cells [BMSCs]) [7, 8], many reports have now described the presence of MSCs in a variety of fetal, perinatal, and adult tissues, including peripheral blood, umbilical cord Wharton's jelly (WJ-MSCs) and blood (UCB-MSCs), fetal liver and

lungs, adipose tissue (AT-MSCs), skeletal muscles, amniotic fluid, synovium, and the circulatory system, where they work as supportive cells and maintain tissue homeostasis [9, 10]. More interestingly, it has been shown that MSCs are able to "transdifferentiate" into cells with endodermal or ectodermal characteristics and particularly into neuron-like cells [11, 12].

Despite the establishment of precise criteria that generally define MSCs [13], the major issue regarding those cells resides in the lack of exact and specific phenotypic characterization, since no specific and unique MSC marker has been reported so far. Indeed, MSCs may display different features depending on which animal species and tissue source they are isolated from, whereas differences in culture media formulations, plating density, and oxygen tension may also affect the phenotype of the mesenchymal population. Consequently, several groups described MSCs with a wide variety of different phenotypes: Verfaillie's group [14, 15] described a rare population of cells in the human bone marrow stroma as mesodermal adult progenitor cells (MAPCs), and D'Ippolito et al. [16, 17] characterized marrow isolated adult multilineage inducible cells after culturing them in low oxygen tension, whereas a lot of other groups kept the mesenchymal stem cell concept as defined by Pittenger et al. [18].

In addition to the phenotypic differences of MSCs, which are mostly inherent to experimental settings, it has been demonstrated that some adult MSC locations contained mixed populations of cells arising from different embryonic lineages. Indeed, in the past few years, multipotent and self-renewing NCSCs have been described to persist in the adult organism. Those postmigratory NCSCs were found in the sciatic nerve [19], the gut [20], the skin (skin-derived precursors [SKPs] and epidermal NCSCs [EPI-NCSCs]) [21–23], the cornea [24], the heart [25], the teeth (dental pulp stem cells [DPSCs]) [26], the palate [27], the carotid body [28], the dorsal root ganglion [23], and the bone marrow [23, 29].

The properties of self-renewal and multilineage differentiation ability of all the described stem cells make them truly attractive candidates for cell therapy. Furthermore, some of them offer the big advantage of being easily obtained without invasive methods. Indeed, umbilical cord is usually discarded and could rather be preserved in order to collect UCB-MSCs and WJ-MSCs, and bone marrow aspiration (BMSCs), lipo-aspiration (AT-MSCs), skin biopsy (SKPs and EPI-NCSCs), and tooth extraction (DPSCs) are noninvasive procedures that are commonly performed in a clinical context. Those procedures could even be performed in patients when needed, allowing autologous grafts and avoiding immunological issues. Additionally, the use of MSCs/NCSCs, either from adult origin or isolated from umbilical cord, get round the ethical problems related to fetal cell use. Finally, those cells are supposed to be safer than ES cells or iPS cells in terms of tumorigenicity and genomic modifications [30].

Neural Differentiation of MSCs and NCSCs: Are Real Neurons Generated?

At the molecular level, a lot of induction protocols indicate that many signaling pathways may be involved in the neural fate of MSCs and NCSCs [31–58]. Indeed, the signalization pathways involving cAMP, retinoic acid, Hedgehog, Wnt, and the neurotrophin-activated pathways have been linked with the maturation of adult MSCs/NCSCs into cells with neural features. After an induction process consisting of various activators, lengths, and conditions of culture, MSCs/NCSCs adopt a neural morphology and express markers (at the transcriptome as well as the protein level) that are usually used to characterize neurons at different developmental stages (Table 1).

Still, the relevance of those markers is currently matter of debate, since the expression of some neural-associated proteins is observed during mesenchymal differentiation [59] and even in different primary cultures of human bone marrow stromal cells [60, 61]. Proper neural differentiation therefore becomes ambiguous, because it is rarely expressed as a percentage of positive cells compared with basal conditions.

Additionally, despite the expression of those "specific" neural markers, only a tiny number of in vitro protocols were able to provide convincing evidence for a neuron-specific electrophysiological signature of the differentiated cells. During neural development, immature neural cells undergo a differentiation process toward functional neurons through different stages that are accurately defined by specific electrophysiological features [62]. Briefly, the first currents that occur in the cell consist of voltage-dependent outward potassium currents. As maturation proceeds, voltage-dependent inward calcium and sodium currents arise sequentially. The ultimate step is finally characterized by the elicitation of action potential through the activity of several mature voltage-gated sodium channels: an important depolarization triggers intracellular modifications, protein activation, and vesicular trafficking that are required for proper synaptic chemical and electrical function/transmission. As clearly observed in Table 1, even if a few data attest to primary electrophysiological activity in MSC/NCSC-derived neuron-like cells (as shown by sodium and potassium currents), there is not sufficient evidence for action potential firings and for an appropriate neuronal function [63].

Overall, we tend to conclude that although the cells express neural-specific proteins and exhibit a preliminary electrical activity, MSCs and NCSCs do not seem to be able to fully differentiate and generate functional neurons in vitro in a sufficient yield, in order to join the objective of cell-based therapy in human neurological treatments.

Adult MSC- and NCSC-Based Therapies in Animal Models for Neurological Diseases

Mesenchymal stem cells and their neural crest-derived neighbors are not only endowed with high multipotentiality but also present other endogenous properties that still make them interesting in cell therapy [64, 65]. First of all, they are able to strongly modulate immune responses, as first shown by improvements of graft-versus-host disease manifestations that were observed after hematopoietic cell transplantation [66] (for a more complete review, see [9]). Because they secrete a wide range of factors, MSCs/NCSCs also constitute ideal trophic support for cell survival, proliferation, and differentiation [67–70]. Finally, it has been shown that they are able to stimulate or recruit endogenous cells/progenitors when transplanted into the brain [71], indicating that they can act on the host environment through indirect pathways. In the next part of this review, we will review and list most of the recent and available studies describing the effect of MSCs/NCSCs in various animal models of neurological diseases (Table 2).

Table 1. In vitro protocols for neural differentiation of different types of MSCs/NCSCs and detailed results

	Cell type	Passage	Pathway	Induction protocol	Protocol length	Neural phenotype	Electrophysiological profile	Inhibitor	Reference
1	UCB-MSCs	ns	cAMP-PKA-CREB	Forskolin	1–7 days	NF, GFAP	No	H89, U0126	[52]
2	BMSCs	P12–P24	cAMP-PKA-CREB, NT	(1) EGF, bFGF; (2) cAMP, IBMX, BDNF	(1) 1 week; (2) 12 hours	NF-200, NF-M, NeuroD, MAP2, NeuN, GABA	Inward Na^+ currents and outward K^+ currents	PKAi fragment 6–22 amide	[41]
3	BMSCs	P3–P6	cAMP-PKA-CREB	GM-CSF	6–96 hours	Nestin, NSE, GFAP	No	No	[44]
4	BMSCs	P0?	cAMP-PKA	Forskolin, IBMX	1 hour to 2 days	βIII-tubulin, GFAP, NSE	No	H89	[55]
5	BMSCs	ns	cAMP	Forskolin/8-bromo-cAMP	6 and 24 hours/1 and 4 days	βIII-tubulin	No	No	[47]
6	BMSCs	ns	NT, SHH	SHH, FGF8, bFGF (+ BDNF)	12 days	NeuN, TH, βIII-tubulin, DAT	Inward Na^+ currents and outward K^+ currents	No	[51]
7	BMSCs	P3–P8	cAMP, RA, SHH	Forskolin, SHH and/or RA	2 days	Nestin, Sox2, NSE, GFAP, synapsin, ACh	Neuronal resting potential	No	[46]
8	BMSCs	P3–P5	cAMP, NT, RA, SHH	(1) bFGF, forskolin; (2) forskolin, IBMX, RA, SHH, BDNF	7 days	GATA3, Sox10, GluR4, Irx2, calretinin, MAP2, NeuN, βIII-tubulin	No	No	[38]
9	MIAMI cells	P3–P9	cAMP, NT, RA, SHH	(1) bFGF; (2) NT-3, SHH, RA, FGF8; (3) forskolin, NT-3, BDNF, NGF, GDNF.	(1) 24 h; (2) 2 days; (3) 3–7 days	NSE, GFAP, βIII-tubulin, NF-L, NF-M, Nurr1, TH	Inward Na^+ currents and outward K^+ currents	No	[49]
10	AT-MSCs	ns	cAMP, NT, RA, SHH	(1) bFGF, IBMX; (2) SHH, RA; (3) BDNF, GDNF	(1) 6 hours; (2) 1 week; (3) ns	βIII-tubulin, ChAT, Nkx2.2, Pax6, Hb9, Olig2	No	No	[45]
11	UCB-MSCs	P5–P8	cAMP-PKA, NT, RA	RA, IBMX, NGF, bFGF	8 hours to 7 days	GFAP, NF-L, NF-M, NF-H, NSE, Nurr-1, TH, Tau	No	H89	[50]
12	BMSCs	P4	cAMP, PKC, RA	Forskolin, IBMX, TPA/RA	Up to 48 hours/7 days	βIII-tubulin, GFAP, NSE, NF-M	No	No	[48]
13	BMSCs	P3–P4	cAMP, RA (RARβ)	(1) RA; (2) forskolin	(1) 24 hours; (2) ns	Nestin, NSE, MAP2	Neuronal resting potential	No	[58]
14	DPSCs	P0?	RA	(1) EGF, bFGF; (2) bFGF; (3) bFGF, RA	(1) 7 days; (2) 7 days; (3) 7 days.	Nestin, βIII-tubulin, NF-M, NF-H, PSA-NCAM	Inward Na^+ currents	No	[26]
15	MIAMI cells	P5–P9	cAMP, NT	(1) EGF, bFGF; (2) bFGF; (3) bFGF, NT-3; (4) (3) forskolin, NT-3, BDNF, NGF.	(1) 10 days; (2) 24 hours; (3) 2 days; (4) 3 days	βIII-tubulin, NF-M, NF-H, NF-L, GalC	No	No	[32]
16	MIAMI cells	ns	NT (TrkC)-Rac1-MEK1/2-ERK1/2	(1) bFGF; (2) NT-3.	(1) 24 hours; (2) 48 hours	βIII-tubulin, NF-M, NF-H, NF-L, Nestin	No	U0126, K252a, NSC23766	[33]
17	SKPs	P3–P9	NT	(1) bFGF, EGF; (2) NT-3, NGF, BDNF	(1) 2–3 weeks; (2) 2–3 weeks.	NF-M, GAP43, βIII-tubulin, MAP2	No	No	[21]
18	BMSCs	P5 NCSC clones	MAPKs	Coculture with CGN	5 days	βIII-tubulin	Inward Na^+ currents and outward K^+ currents (PA for BM-MSCs clones)	PD98059	[53]
19	SKPs	ns	NT	(1) bFGF, EGF; (2) NGF	ns	NF-M, βIII-tubulin, GFAP	No	No	[31]
20	UCB-MSCs	ns	NT-Raf1-MAPK/ERK, RA	bFGF, RA, BDNF	7 days	βIII-tubulin, NeuN, GFAP, MBP	No	LY294002, PD98059	[43]
21	UCB-MSCs	ns	NT (TrkB)-Raf1-MAPK-ERK, B-catenin	BDNF gene transfection		βIII-tubulin, NeuN, GFAP, MBP	No	K252A	[42]
22	WJ-MSCs	P3	NT	BDNF/HCNP/rDHE	14 days	MAP2, ChAT	No	No	[56]
23	AT-MSCs	ns	cAMP-NT	(1) bFGF, EGF, BDNF; (2) IBMX	(1) 3 days; (2) 48 hours	βIII-tubulin, GFAP	No	No	[54]
24	BMSCs and DPSCs	P3	cAMP-NT	bFGF, EGF, BDNF, IBMX	3–5 days	GFAP, c-fos, NF, HNK1, enolase-2, βIII-tubulin, MAP2, Sox2, Tenascin-C, Connexin-43, nestin	No	No	[35]
25	DPSCs	P1–P4	cAMP, PKC, RA	(1) bFGF, 5-azacytidine; (2) bFGF, IBMX, TPA, db-cAMP, forskolin, NT-3, NGF; (3) db-cAMP, NT-3	(1) 48 hours; (2) 3 days; (3) 3–7 days	βIII-tubulin, NF-M, GFAP, NeuN, NSE	Inward Na^+ currents and outward K^+ currents	No	[37]
26	SKPs	P3	NT, RA	(1) RA; (2) NT-3	(1) 7 days; (2) 7 days	βIII-tubulin, GFAP, MAP-2, NeuN	No	K252a, Pep5	[57]
27	SKPs	ns	cAMP, NT, RA	(1) RA, NT-3, BDNF, NGF, db-cAMP	2 weeks to 1 month	PGP9.5, NF, NMDAR	No	No	[40]

Table 1. (*Cont'd*)

	Cell type	Passage	Pathway	Induction protocol	Protocol length	Neural phenotype	Electrophysiological profile	Inhibitor	Reference
28	BMSCs	P3–P4	cAMP-MAPK-MEK-ERK-Raf	Forskolin	48 hours	βIII-tubulin, NF200, NSE	No	PD98059	[36]
29	BMSCs	ns	cAMP-PKA, PKC, MAPK-MEK-ERK	(1) bFGF; (2) forskolin	(1) Overnight; (2) Up to 7 days	NF	No	K252a, KT5720, AG879, KN-62, LY294002, PD98059	[34]
30	BMSCs	P0?	cAMP-Wnt	bFGF, IBMX, forskolin, Wnt1	3–7 days	Ngn1, Brn3a, NeuroD, P2X3, GluR2, GluR4	No	No	[39]

ns indicates that the passage or the incubation length is not specified. "No" indicates that no electrophysiological results are described in the study or that no inhibitor has been tested to confirm the pathway. The inhibitors are as follows: AG879, Trk receptor inhibitor; H89, PKA inhibitor; K252a, kinase inhibitor; KN-62, Ca^{2+}/calmodulin-dependent protein kinase inhibitor; KT5720, PKA inhibitor; LY294002; PI3K inhibitor; NSC23766, Rac1 inhibitor; PD98059, MEK inhibitor; Pep5, p75 neurotrophin receptor inhibitor; PKA inhibitor fragment 6–22 amide, PKA inhibitor; U0126, MEK inhibitor.

Abbreviations: Ach, acetylcholine; AT-MSC, adipose tissue mesenchymal stem cells; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; BMSCs, bone marrow stromal cells; Brn3a, brain-specific homeobox/POU domain protein 3A; CGN, cerebellar granule neurons; ChAT, choline acetyltransferase; CREB, cAMP-responsive element-binding protein; DAT, dopamine transporter; db-cAMP, dibutyryl-cAMP; DPSCs, dental pulp stem cells; EGF, epidermal growth factor; ERK, extracellular regulated kinase; FGF8, fibroblast growth factor 8; GalC, galactocerebrosidase; GAP43, growth-associated protein 43; GATA3, trans-acting T-cell-specific transcription factor; GDNF, glial cell line derived growth factor; GFAP, glial fibrillary acidic protein; GluR2, metabotropic glutamate receptor 2; GluR4, metabotropic glutamate receptor 4; GM-CSF, granulocyte/macrophage colony stimulating factor; Hb9, motor neuron and pancreas homeobox 1 (MNX1); HCNP, hippocampal cholinergic neurostimulating peptide; HNK1, human natural killer 1; IBMX, 3-isobutyl-1-methylxanthine; Irx2, Iroquois-class homeodomain protein IRX-2; MAP2, microtubule-associated protein 2; MAPK, mitogen-activated protein kinase; MBP, myelin basic protein; MEK, mitogen-activated protein kinase kinase; MIAMI, marrow isolated adult multilineage inducible; MSC, mesenchymal stem cell; NCSC, neural crest stem cell; NeuN, neuronal nuclear antigen; NF, neurofilament; NGF, nerve growth factor; Ngn1, neurogenin 1; Nkx2.2, homeobox protein Nkx-2.2; NMDAR, *N*-methyl-D-aspartate receptor; NSE, neuron-specific enolase; NT, neurotrophin pathway; NT-3, neurotrophin-3; Nurr1, nuclear receptor-related 1 protein; P, passage; P2X3, P2X purinoceptor 3; Pax6, paired box protein 6; PGP9.5, ubiquitin carboxy-terminal hydrolase L1; PKA, protein kinase A; PKAi, PKA inhibitor; PKC, protein kinase C; PSA-NCAM, polysialated neural cell adhesion molecule; RA, retinoic acid; Rac1, Ras-related C3 botulinum toxin substrate 1; Raf1, RAF proto-oncogene serine/threonine-protein kinase; rDHE, rat denervated hippocampal extract; SHH, sonic hedgehog, SKP, skin-derived precursor; Sox10, SRY (sex-determining region Y)-box 10; Sox2, SRY (sex-determining region Y)-box 2; TH, tyrosine hydroxylase; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; TrkC, tropomyosin-related kinase receptor C; UCB-MSCs, umbilical cord blood mesenchymal stem cells; WJ-MSCs, Wharton's jelly mesenchymal stem cells.

Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia; approximately 26 million people worldwide were affected in 2006 [72]. This pathology is characterized by a progressive degeneration of neurons in the frontal, temporal, and limbic lobes and is associated with the appearance of extracellular plaques (β-amyloid [Aβ] peptide deposits) and neurofibrillary tangles inside neurons (mostly composed of phosphorylated Tau proteins, which are microtubule-associated proteins). As the disease progresses, clinical symptoms include mood swings, irritability and aggressive behavior, language troubles, and memory loss. Because no efficient treatment is available so far, we could ask about the usefulness of stem cell therapy to rescue/prevent neural loss in AD patients. Whereas clinical trials are currently ongoing, several preclinical studies have been performed using AD animal models. The transplantation of UCB-MSCs induced neprilysin (an Aβ-degrading enzyme) expression in host microglia through the secretion of soluble intracellular adhesion molecule-1 (sICAM-1). This neprilysin expression stimulation is followed by a decrease in Aβ42 plaques into the hippocampus of double transgenic APP/PS1 mice (which coexpress the K670N/M671L-mutated amyloid precursor protein and L166P-mutated presenilin 1) [73].

BMSC [74] and UCB-MSC [75] injection into the hippocampus of APP/PS1 mice improved learning and memory impairments and reduced the number of Aβ aggregates through the alternative activation of host microglial cells. Furthermore, the cell transplantation was followed by a decrease of Tau phosphorylation rate. Those researchers further observed that the grafted BMSC release of CCL5 was increased into the brains of APP/PS1 mice and that alternative activation of microglia was associated with elevated CCL5 expression [76]. Moreover, they discovered that endogenous BM cells were also recruited into the brain by CCL5 and took part in inducing microglial activation.

Learning, memory, and pathology in Tg2576 mice (expressing human APP695 isoform with double mutation K670N/M671L) greatly improved after intravenous/intracerebral injection of AT-MSCs. Moreover, the number of amyloid plaques and Aβ levels decreased significantly following AT-MSC graft. This was associated with a rescue of memory impairments and neuropathology and with the up-regulation of neurotrophic factors and interleukins into the AT-MSC-injected AD brains [77].

An increased number of hippocampal neurons were observed after transplantation of nerve growth factor (NGF)-overexpressing BMSCs [78], and this was coupled with reduced latency in memory tasks. It is still not clear whether the hippocampal neurons were spared or rescued or were newly produced after the cell graft. Moreover, NGF-expressing BMSCs expressed choline acetyltransferase after being transplanted. Regrettably, the effect of NGF overexpression compared with normal BMSCs was not sufficiently pronounced or detailed in the study. Brain-derived neurotrophic factor (BDNF)-overexpressing BMSCs were also tested in a model of AD, whose hippocampal ultrastrucure, learning, and memory were then significantly improved [79]. Finally, BMSCs were shown to improve cognitive and memory tasks in aged rats and in ibotenic acid-treated rats, but no additional details were provided [80].

Table 2. Preclinical studies focusing on MSC/NCSC-based therapy protocols, using different experimental models for neurological disorders

					Consequences		Identified ways						
	Cell type	Disease	Animal model	Cell pretreatment	Histological	Clinical	Neural marker expression	Environment improvement	Trophic support	Rescue/ sparing	Anti-inflammation/ immunomodulation	Endogenous cell recruitment	Reference
1	BMSCs	AD	$A\beta_{1-40}$ peptide injected rat	Nothing	ns	+	Yes	ns	ns	Yes	ns	Yes	[78]
2				NGF overexpression	ns	+	Yes	ns	Yes	Yes	ns	Yes	
3	UCB-MSCs	AD	APP-PS1 mouse	Nothing	+	ns	ns	Yes	Yes	ns	ns	Yes	[73]
4	BMSCs	AD	APP-PS1 mouse	Nothing	+	+	ns	Yes	ns	ns	Yes	Yes	[74]
5	BMSCs	AD	APP-PS1 mouse	Nothing	+	+	ns	Yes	Yes	ns	Yes	Yes	[76]
6	UCB-MSCs	AD	APP-PS1 mouse	Nothing	+	+	ns	Yes	ns	ns	Yes	Yes	[75]
7	AT-MSCs	AD	Tg2576 mouse	Nothing	+	+	ns	Yes	Yes	ns	ns	ns	[77]
8	BMSCs	AD	$A\beta_{25-35}$ peptide injected rat	Nothing	+	+	ns	Yes	ns	ns	ns	ns	[79]
9				BDNF overexpression	+	+	ns	Yes	Yes	ns	ns	ns	
10	BMSCs	AD	Aged rat	Nothing	ns	+	ns	ns	ns	ns	ns	ns	[80]
11			Ibotenic acid injected rat	Nothing	ns	+	ns	ns	ns	ns	ns	ns	
12	WJ-MSCs	PD	6-OHDA rat	NCM, SHH, FGF8	+	+	Yes	ns	ns	ns	ns	ns	[89]
13	BMSCs	PD	6-OHDA rat	bFGF/EGF + SHH, FGF8, GDNF	ns	ns	No	ns	ns	ns	ns	No	[91]
14	BMSCs	PD	6-OHDA rat	bFGF/EGF + forskolin, IBMX, db-cAMP, TPA	+	ns	Yes	ns	ns	ns	ns	ns	[92]
15	BMSCs	PD	6-OHDA rat	bFGF/EGF, db-cAMP, IBMX, RA	+	+	Yes	ns	ns	ns	ns	ns	[93]
16	BMSCs	PD	6-OHDA rat	bFGF/EGF, db-cAMP, IBMX, RA	+	+	Yes	ns	ns	ns	ns	ns	[94]
17	DPSCs	PD	6-OHDA rat	bFGF/EGF	+	+	Yes	ns	ns	ns	ns	ns	[90]
18	BMSCs	PD	6-OHDA rat	Nothing	+	+	No	ns	Yes	Yes	ns	ns	[95]
19	BMSCs	PD	MPTP mouse	Nothing	+	ns	No	Yes	ns	ns	Yes	ns	[97]
20	BMSCs	PD	6-OHDA rat	Nothing	+	ns	ns	ns	Yes	Yes	ns	Yes	[98]
21	BMSCs	PD	MPTP mouse	Nothing	ns	ns	ns	ns	Yes	Yes	ns	Yes	[96]
22	BMSCs	HD	QA mouse	Nothing	+	+	Yes	Yes	ns	Yes	ns	Yes	[103]
23			R6/2-J2 mouse	Nothing	+	No	Yes	Yes	Yes	ns	ns	Yes	
24	BMSCs	HD	YAC128 mouse	Nothing	+	+	ns	ns	ns	ns	ns	ns	[106]
25				BDNF/NGF overexpression	+	+	ns	ns	ns	Yes	ns	ns	
26	BMSCs	HD	3NP rat	Nothing	+	+	No	ns	Yes	ns	ns	ns	[105]
27	BMSCs	HD	QA mouse	bFGF/EGF, db-cAMP, IBMX, PDGF, neuregulin 1-β1/HRG1-β1 EGF domain	+	+	ns	ns	Yes	Yes	ns	ns	[107]
28	BMSCs	HD	N171-82Q mouse	Nothing	+	ns	ns	ns	Yes	Yes	ns	Yes	[104]
29	BMSCs	SCI	Rat with contused SC	RA, db-cAMP, forskolin, IBMX	+	+	Yes	ns	ns	ns	ns	ns	[112]
30	BMSCs	SCI	Rat with contused SC	8-bromo-AMP and Rolipram	+	+	Yes	Yes	ns	Yes	ns	ns	[111]
31	BMSCs	SCI	Rat with transected SC	RA + NT-3 overexpression	+	+	ns	Yes	ns	Yes	ns	ns	[113]

Table 2. (*Cont'd*)

	Cell type	Disease	Animal model	Cell pretreatment	Consequences		Identified ways						Reference
					Histological	Clinical	Neural markers expression	Environment improvement	Trophic support	Rescue/ sparing	Anti-inflammation/ immunomodulation	Endogenous cell recruitment	
32	UCB-MSCs	SCI	Rat with transected SC	Nothing	+	+	No	ns	ns	Yes	ns	ns	[114]
33	SKPs	SCI	Rat with contused SC	bFGF/EGF	+	+	No	Yes	ns	No	ns	Yes	[118]
34				Forskolin, neuregulin-1β	+	+	No	Yes	ns	Yes	ns	Yes	
35	BMSCs	SCI	Rat with contused SC	Nothing	+	No	No	Yes	ns	No	ns	Yes	[119]
36				RA, forskolin, bFGF, PDGFab, heregulin.	+	+	Yes	Yes	ns	Yes	ns	Yes	
37	BMSCs	SCI	Mouse with contused SC	Schwann cell coculture	+	+	ns	Yes	ns	Yes	Yes	Yes	[120]
38	BMSCs	SCI	Rat with contused SC	Nothing	+	+	ns	Yes	Yes	Yes	ns	ns	[117]
39	EPI-NCSCs	SCI	Rat with contused SC	mSCF, bFGF/EGF, NT-3	+	ns	Yes	ns	ns	ns	ns	ns	[110]
40	UCB-MSCs	SCI	Rat with contused SC	Nothing	+	+	ns	Yes	ns	ns	ns	Yes	[115]
41	BMSCs	SCI	Rat with transected SC	Nothing	+	No	No	ns	ns	Yes	ns	ns	[116]
42				BDNF overexpression	+	+	No	ns	ns	Yes	ns	ns	
43	BMSCs	ALS	SOD1-G93A rat	Nothing	+	+	ns	ns	Yes	Yes	No	ns	[124]
44				GDNF overexpression	+	+	ns	ns	Yes	Yes	No	ns	
45	BMSCs	ALS	SOD1-G93A mouse	Encapsulation + GLP-1 overexpression	+	+	ns	Yes	ns	ns	Yes	ns	[127]
46	BMSCs	ALS	SOD1-G93A mouse	Nothing	+	+	ns	Yes	ns	No	Yes	ns	[126]
47	BMSCs	ALS	SOD1-G93A mouse	Nothing	+	+	No	Yes	ns	Yes	Yes	ns	[125]
48	BMSCs (ALS patients)	ALS	SOD1-G93A mouse	Nothing	+	+	ns	ns	ns	Yes	ns	ns	[132]
49	UCB-MSCs	Stroke	MCAO rat	Nothing	+	+	Yes	ns	ns	ns	ns	ns	[147]
50	BMSCs	Stroke	MCAO rat	BDNF/GDNF/CNTF/NT-3 overexpression	+	+	ns	ns	Yes	ns	ns	ns	[144]
51	BMSCs	Stroke	MCAO rat	Nothing	+	+	ns	ns	Yes	ns	ns	ns	[142]
52	BMSCs	Stroke	MCAO mouse	Nothing	No	ns	ns	No	ns	No	ns	No	[149]
53	MAPCs	Stroke	FeCl3-injected mouse	Nothing	+	ns	ns	Yes	ns	Yes	Yes	Yes	[138]
54	BMSCs			Nothing	+	ns	ns	Yes	ns	Yes	Yes	Yes	
55	BMSCs	Stroke	MCAO rat	Survivin overexpression	+	+	Yes	Yes	Yes	Yes	ns	ns	[141]
56	BMSCs	Stroke	MCAO rat	VPA and lithium treatment	+	+	ns	Yes	ns	Yes	ns	ns	[148]
57	WJ-MSCs	Stroke	MCAO rat	Rat brain conditioned medium	+	ns	ns	ns	Yes	ns	ns	ns	[143]
58	DPSCs	Stroke	MCAO rat	Nothing	+	+	Yes	Yes	ns	ns	ns	ns	[140]
59	AT-MSCs	ICH	Collagenase-injected rat	Nothing	+	+	Yes	ns	ns	ns	ns	ns	[146]
60	BMSCs	ICH	Collagenase-injected rat	GDNF overexpression	+	ns	Yes	Yes	ns	ns	ns	ns	[145]
61	AT-MSCs	ICH	Collagenase-injected rat	Nothing	No	+	No	ns	ns	ns	ns	Yes	[139]
62	BMSCs	MS	EAE mouse	Nothing	+	+	Yes	ns	ns	ns	Yes	Yes	[159]
63	BMSCs	MS	EAE mouse	Nothing	+	+	No	ns	ns	Yes	Yes	ns	[153]

Table 2. (*Cont'd*)

	Cell type	Disease	Animal model	Cell pretreatment	Consequences		Identified ways						Reference
					Histological	Clinical	Neural markers expression	Environment improvement	Trophic support	Rescue/ sparing	Anti-inflammation/ immunomodulation	Endogenous cell recruitment	
64	BMSCs	MS	EAE mouse	bFGF/EGF	+	+	ns	Yes	ns	Yes	Yes	Yes	[158]
65	BMSCs	MS	EAE mouse	Nothing	+	+	Yes	Yes	ns	Yes	Yes	ns	[154]
66	BMSCs	MS	EAE mouse	Nothing	+	+	Yes	Yes	Yes	ns	Yes	ns	[155]
67	BMSCs	MS	EAE mouse	Nothing	+	+	Yes	ns	Yes	Yes	ns	ns	[157]
68	UCB-MSCs	MS	EAE mouse	Nothing	+	+	ns	Yes	ns	ns	Yes	ns	[156]

A plus sign indicates improvement. "Yes" indicates that the value has been confirmed. "No" indicates not observed, and ns indicates not specified/tested.

Abreviations: 3NP, 3-nitropropionic acid; 6-OHDA, 6-hydroxydopamine; Aβ, Aβ-amyloid peptide; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AT-MSCs, adipose tissue-mesenchymal stem cells; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; BMSCs, bone marrow stromal cells; CNTF, ciliary neurotrophic factor; db-cAMP, dibutyryl-cyclic adenosine monophosphate; DPSCs, dental pulp stem cells; EAE, experimental autoimmune encephalomyelitis; EGF, epidermal growth factor; EPI-NCSCs, epidermal neural crest stem cells; FGF8, fibroblast growth factor 8; GDNF, glial cell line-derived neurotrophic factor; GLP-1, glucagon-like peptide 1; HD, Huntington's disease; IBMX, 3-isobutyl-1-methylxanthine; ICH, intracerebral hemorrhage; MAPCs, multipotent adult progenitor cells; MCAO, middle cerebral artery occlusion; MPTP, 1-methyl-4-phenyltetrahydropyridine; MS, multiple sclerosis; MSC, mesenchymal stem cell; mSCF, murine stem cell factor; NCM, neural-conditioned medium; NCSC, neural crest stem cell; NF, neurofilament; NGF, nerve growth factor; NT-3, neurotrophin-3; PD, Parkinson's disease; PDGF, platelet-derived growth factor; QA, quinolinic acid; RA, retinoic acid; SC, spinal cord; SCI, spinal cord injury; SHH, sonic hedgehog; SKP, skin-derived precursors; SOD1, superoxide dismutase 1; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; UCB-MSCs, umbilical cord blood mesenchymal stem cells; VPA, valproic acid; WJ-MSCs, Wharton's jelly mesenchymal stem cells.

Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, with a prevalence of 0.3% of the population in industrialized countries, reaching 1% after 60 years of age [81]. This pathology is characterized by typical clinical symptoms such as bradykinesia, rigidity, gait troubles, and resting tremor. The main pathological feature is the loss of dopaminergic neurons in the substantia nigra pars compacta, associated with accumulation of ubiquitinated protein aggregates called Lewy bodies in different locations of the brain [82, 83]. In the early 1990s, clinical trials were started using fetal mesencephalic dopaminergic neuroblasts to transplant in PD patients [84–86]. Despite the demonstration of several durable benefits in terms of clinical symptoms and pathology, a few problems remain. Fetal tissue heterogeneity, influence of harvesting methods on the graft efficiency, need of too many fetuses for only one patient, and absence of immunosuppression in an allograft procedure, all coupled with ethical concerns, left no option but finding other ways to proceed.

More recently, a clinical trial described unilateral transplantation of autologous BMSCs into the subventricular zone (SVZ) of PD patients, and reported moderate clinical improvement with no adverse effects, such as tumor formation [87, 88]. Those results were based on clinical observations and Unified Parkinson's Disease Rate Scale scores, and the mechanisms underlying the reported ameliorations are completely unknown.

Neural differentiation-based therapy protocols were performed using MSCs/NCSCs from Wharton's jelly [89], dental pulp [90], and bone marrow [91–94] that underwent neural induction before being transplanted into 6-hydroxydopamine-treated rats. Behavioral and pathological enhancements were observed in most of the studies, but except for the rare expression of some neural markers (that were already observed in few cells in vitro), the underlying mechanisms were not sufficiently detailed. Conversely, significant improvements were observed in PD animal models that were transplanted with BMSCs without any pretreatment. Whereas no sign of differentiation was observed, beneficial effects and rescue of dopaminergic neurons were mainly associated with trophic support (i.e., glial cell line neurotrophic factor [GDNF] or epidermal growth factor [EGF] secretion) [95, 96] or anti-inflammation (attenuation of blood-brain barrier damage or microglia inactivation) [97]. Moreover, BMSC graft induced proliferation and migration of endogenous SVZ neuroblasts models of PD [96, 98].

Huntington's Disease Models

Huntington's disease (HD) is caused by an autosomal dominant mutation in either of an individual's two copies of a gene called Huntingtin (Htt) (expansion of polyglutamine encoded by CAG repeats in exon 1 of the *IT15* gene). This neurodegenerative disorder typically becomes noticeable at midlife, affects muscle coordination, and leads to cognitive decline and psychiatric problems [99]. Although the exact mechanism underlying HD progression remains uncertain, its hallmarks are an important atrophy of the striatum and cortex and a decrease in the number of striatal GABAergic neurons [100]. So far, only fetal neural cells allografts have been performed with HD patients, whose cognitive and motor functions were moderately improved [101, 102]. Lately, a group studied the impact of BMSC transplantation in two different models of HD, the quinolinic acid (QA)-lesioned

mouse and a genetically modified R6/2-J2 mouse (exon 1 from Htt and 144 CAG repeats) [103]. All of the transplanted mice survived longer than controls, and despite a slight expression of neural markers by few cells, the environmental improvement and the rescue of neurons and locomotor activity was mainly associated with neurotrophic support. Indeed, grafted cells increased the expression of stromal-derived factor-1 (SDF-1) and von Willebrand factor in the lesioned tissue, whereas they decreased the expression of Bax and caspase-3, suggesting proangiogenic and antiapoptotic events. Additionally, transplanted BMSCs induced neuroblast migration (doublecortin positive cells) into the lesioned striatum. The same observations were carried out with another genetic model for HD, the N171-82Q mouse [104]. After BMSC graft, the reduction of striatal atrophy was coupled with fibroblast growth factor-2 (FGF2 or bFGF), ciliary neurotrophic factor, NGF, and vascular endothelial growth factor (VEGF) secretion, and recruitment of endogenous neural cells was observed too. According to Rossignol et al. [105], BDNF secretion was detected in the brains of BMSC-transplanted 3-nitropropionic acid-injected rats, coupled with behavioral sparing and reduction in ventricle enlargement, whereas no sign of neural differentiation was observed. Functional benefits were also observed after transplantation of BDNF/NGF-secreting BMSCs in YAC128 mice [106]. The importance of trophic support for HD management is reinforced by another study that describes a significant improvement in QA toxicity after transplantation of neurotrophic factor-secreting BMSCs [107]. More importantly, they showed that BMSCs derived from HD patients can also be induced to secrete neurotrophic factors and exert efficacious effects similarly to cells derived from healthy donors.

Spinal Cord Injuries

Whereas peripheral nerves are able to regenerate after lesion, the motoneurons and nervous fibers in the spinal cord cannot be replaced in case of spinal cord contusion, section, or compression. Traumatic spinal cord injury (SCI) results in a wide panel of physiopathological events counteracting any possibility of neural regeneration, and those events are generally grouped in two phases. The primary injury phase is characterized by section of axons, necrosis, degeneration, oligodendrocyte apoptosis, gliosis, and macrophage infiltration. Altogether, those events lead to secondary lesions like ischemia, inflammation, alteration of ionic balance, insults of the blood-brain-barrier, lipid peroxidation, and glutamate-induced excitotoxicity. Despite a slight spontaneous recovery, all those events collectively constitute an environment that hampers axonal regeneration [108]. Because the clinical consequences of such lesions are dramatic and rarely reversible (paraplegy, hemiplegy, tetraplegy, respiratory problems, and loss of sphincter control, all leading to important socioeconomic issues), it is crucial to find efficient therapies to improve the recuperation of motor function. Recent clinical applications highlighted a tendency for BMSCs to enhance recovery after SCI [109], but this effect was not significant, and further investigation has to be performed in order to attest to a real clinical benefit.

Some studies focusing on SCI therapy are also based on the graft of predifferentiated MSCs/NCSCs. They highlighted the expression of neural markers (such as microtubule-associated protein 2, neuron-specific enolase, nestin, and βIII-tubulin) in grafted BMSCs/EPI-NCSCs and showed significant improvements in terms of cystic cavity size, neural loss [110], and motor performance [111–113]. On the other hand, enhancement of functional locomotor abilities was observed [114, 115] after transplantation of unrestricted UCB-MSCs into the surrounding area of a hemisection injury, accompanied by cell accumulation near the lesion, reduction in its size, enhanced axon regrowth, and endogenous cell proliferation. In the same way, rescue of neurons coupled with pathological and behavioral improvements were observed after graft of BDNF-hypersecreting BMSCs [116] without any pretreatment and any sign of in vivo differentiation, suggesting a trophic role for grafted cells. NGF also seems to be involved in SCI motor recovery and tissue sparing, as shown [117]. Moreover, they demonstrated the proangiogenic function of VEGF secretion by grafted BMSC.

Glial cell-based therapy also makes sense regarding SCI treatment. A couple of papers have compared nondifferentiated SKP/BMSCs with SKP/BMSC-derived Schwann cells (SchCs) [118, 119]. Modifications of the lesioned environment and motor improvements were much more dramatic using SKP/BMSC-SchCs than nondifferentiated cells. Indeed, results revealed that both cell types reduced the size of the contusion cavity, myelinated endogenous host axons, and recruited endogenous SchC. More interestingly, SKP-SchC also provided a bridge across the lesion site, increased the size of spared tissue, myelinated spared axons, reduced gliosis, and provided an environment that was highly conducive to axonal growth. Finally, SKP/BMSC-SchC provided enhanced locomotor recovery relative to native cells. In the same way, cocultivating BMSCs with SchC improved their therapeutic effects in spinal cord-injured mice [120].

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is characterized by a progressive and selective degeneration of motoneurons whose cell bodies are present in the spinal cord, in motor nuclei of cranial nerves and in motor cortex, inducing muscular atrophy with a pyramidal syndrome and leading irreversibly to death. To date, pharmalogical treatments (for example, riluzole) only moderately prolong the survival of patients. Most ALS cases are sporadic, but approximately 10% are hereditary, based among others on the transmission of mutations in the copper/zinc superoxide dismutase (*SOD1*) gene that induce death of motoneurons by a gain of toxicity.

Whereas trials already confirm that autologous BMSC transplantation is safe [121, 122] and seems to be applicable in a clinical context, studying SOD1 transgenic animals may provide a better understanding of pathogenic mechanisms and testing of therapies for ALS. A potent effect of trophic support, and more specifically of GDNF, on ALS lesions was recently highlighted. Therefore, GDNF-engineered BMSCs were transplanted into the tibial muscles of SOD1-G93A rats and prolonged the survival of treated animals [123, 124]. After transplantation, the number of denervated neuromuscular junctions was reduced as the number of innervated ones was increased. Grafted cells also prevented the loss of cholinergic neurons in the ventral horn of spinal cord. The anti-inflammatory properties of BMSCs seem also to be important as concerns ALS therapy. Indeed, neuroinflammation (both astrogliosis and microgliosis) was reduced after BMSC administration in SOD1-G93A mice, who exhibited better behavioral performances [125], whereas only $<1\%$ of grafted cells expressed neural markers. Likewise, BMSC administration reduced ubiquitin inclusions, astrogliosis, microgliosis, oxidative

stress, and excessive release of glutamate, also resulting in better clinical features, which did not rely on a long-term integration of grafted cells or on a rescue of cholinergic neurons [126].

Glucagon-like peptide 1-modified BMSCs reduced spinal cord astrogliosis and microgliosis when injected into the cerebral ventricles of SOD1-G93A mice, then ameliorating survival and delaying deterioration onset, associated with better motor performances [127].

Because it was previously shown that BMSCs isolated from SOD1-G93A rats exhibited reduced neuroprotective abilities in vitro [128], the question of an efficient autologous cell graft in ALS patients was raised. A couple of preclinical studies have been performed using MSCs from ALS patients, in order to attest to their safety and efficacy. Whereas some studies attest to a decreased functionality and trophic support of ALS patients' BMSCs [129, 130], suggesting that allogeneic graft would be a better way, other papers focused on setting up precise conditions for using autologous BMSCs. In this context, BMSCs from early passages were suggested to be safer and more suitable for cell therapy [131]. Furthermore, 1×10^6 BMSCs (from ALS patients) was shown to be the optimal dose to administer in SOD1-G93A mice [132] in order to observe prolonged survival and improved motor performances together with a lesser extent of neural loss.

Ischemic Stroke and Intracerebral Hemorrhage

Cerebral infarct or stroke is characterized by the rapid loss of brain functions after a local stop in blood supply. This can be due to ischemia (lack of blood flow) caused by thrombotic or embolic blockage or due to intracerebral hemorrhage (ICH). In this last case, the expanded lesion volume could also be responsible for a local and peripheral ischemic insult. As a result, the affected brain area has impaired function, metabolism, and connections, which results in an inability to move, to understand or formulate speech, or to see a complete visual field (regarding the localization of the lesion).

Despite the advances in clinical management, stroke continues to pose major therapeutic challenges since it remains the second most common cause of death worldwide [133], and increasing experimental data now suggest that cell transplantation could considerably enhance recovery. Indeed, intravenous administration of autologous MSCs in patients with severe stroke seems to improve pathological and functional recovery without important side effects [134–136]. Another clinical study noticed that clinical improvement was associated with SDF-1 concentrations in patients' sera [137].

On the other hand, preclinical studies are required to further detail pathways that are linked to this beneficial effect of MSC. As shown by Mora-Lee et al. [138], BMSCs and MAPCs are both able to induce benefits in terms of tissue sparing after $FeCl_3$-induced stroke, through the inactivation of microglia, reduction of glial scar formation, and initiation of angiogenesis. Additionally, increased proliferation and survival of SVZ neuroblasts were observed in those conditions. Recruitment of endogenous cells was also described [139], which was the only explanation of the improvement in Rotarod performances that was seen after AT-MSC transplantation in a model of collagenase-induced ICH. DPSCs also seem able to promote recuperation after ischemic stroke, when transplanted into the brain of rats with middle cerebral artery occlusion (MCAO) [140]. Neurobehavioral and sensorimotor functional recovery, as well as the reduction in tissue atrophy, were rather associated with glial fate adoption than with neural differentiation of injected DPSC.

Secretion of neurotrophic molecules (like BDNFs, GDNFs, and bFGFs, among others) and antiapoptotic factors by WJ-MSCs or BMSCs was studied by different groups [141–144] and demonstrated to play a key role in pathological and clinical recovery of MCAO rats and collagenase-treated rats [145]. Whereas some more papers describe significant improvements on pathological and behavioral aspects [146–148], one study showed that systemically grafted BMSCs integrated peripheral organs but failed to induce any change in sparing lesioned brain tissue and environment, whereas no recruitment of endogenous cells was detected [149].

Multiple Sclerosis

Multiple sclerosis (MS) is a common neurological disease and a major cause of disability, particularly affecting young adults. It is characterized by patches of damage occurring throughout the brain and spinal cord with loss of myelin sheaths accompanied by loss of oligodendrocytes [150]. Although the cause of MS remains unidentified, an autoimmune reaction against oligodendrocytes and myelin is generally assumed to play a major role, and early acute MS lesions almost invariably show prominent inflammation.

Recent clinical trials showed evidence for the safety and benefit of autologous BMSCs [151] that were injected in MS patients, whose visual functions and optic nerve structure were enhanced after treatment [152, 153]. Efforts to develop cell therapy for CNS lesions in MS have long been directed toward implanting cells capable of replacing lost oligodendrocytes and regenerating myelin sheaths, yet this strategy is now more discussed. Indeed, most of the recent preclinical studies suggest that the BMSCs' most prominent properties with regard to MS are their important ability to modulate immunity and inflammation, through the regulation of T-cell activity for the most part [154–156]. This immunomodulatory effect was highlighted in MS patients who received intravenous injection of BMSCs and afterward exhibited improved neurological functions [121]. It was lately shown that UCB-MSCs also present immunoregulatory properties and promote remyelination and clinical recovery when administered to mice with experimental autoimmune encephalomyelitis (EAE) [157]. Besides, other preclinical studies highlight the role of neuroprotective and pro-oligodendrogenic molecule secretion by grafted cells. NGF-secreting cells were detected after graft of BMSCs in EAE mice [158], and other studies showed the involvement of spinal cord endogenous progenitors in de novo oligodendrogenesis [159, 160]. Recently, hepatocyte growth factor secreted by MSCs (detected in conditioned medium) was demonstrated to be a chief actor in MS lesion recovery [161] (for more exhaustive reviews, see [162, 163]).

Conclusion

Altogether, these numerous studies highlight the strengths and weaknesses of MSCs/NCSCs as candidates for cellular therapy in neurological disorders. (a) Adult MSCs/NCSCs have a limited capacity to differentiate into fully mature neurons able to fire action potentials in culture under various conditions of stimulation, suggesting that those cells may not be good candidate for cell replacement therapy. (b) On the other hand, when transplanted in various animal models mimicking neurological diseases, adult

MSCs/NCSCs improve the recovery and/or the clinical situation of these animals, but without properly integrating the CNS and differentiating into new neurons. The grafted cells are mostly acting through the secretion of various factors (more or less described) able to modulate the inflammatory reaction, the glial scar, the neuronal cell survival, and the remyelination and/or recruitment of the host glial cells and neural stem cells. A fine analysis of the secretome of MSCs/NCSCs would therefore be mandatory in order to develop protocols aiming to pharmacologically mimic the effect of grafting procedures. Altogether, it appeared that MSCs/NCSCs have a dual purpose to develop model systems in the discovery of novel single/combinatorial pharmaceutical treatments and cell therapy protocols for a range of neurological diseases.

Author Contributions

V.N.: conception and design, collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; C.C.: final approval of manuscript; B.R.: conception and design, financial support, final approval of manuscript; S.W.-G.: conception and design, data analysis and interpretation, manuscript writing, final approval of manuscript.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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Concise Review: Adult Mesenchymal Stem Cells, Adult Neural Crest Stem Cells, and Therapy of Neurological Pathologies: A State of Play

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