Adult mesenchymal stem cells in neural regeneration and repair: Current advances and future prospects (Review)

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Abstract. Mesenchymal stem cells (MSCs) are an attractive cell source for regenerative medicine as they can be easily isolated from bone marrow (BM) aspirates and expanded in culture while maintaining their 'stemness'. In addition to differentiating into mesodermal cells, MSCs have shown considerable plasticity and generate ectodermal neurons and glia, which can be used to replace cells damaged by neurological diseases and injuries. These unique stem cells also exhibit immunomodulatory functions and secrete a variety of trophic factors which support regeneration and repair. This review focuses on the therapeutic usage of MSCs for neurodegenerative diseases and traumatic injuries to the nervous system. Animal studies demonstrate great promise for MSC transplantation in neurological disorders. In fact, a few clinical trials have already been initiated and show that MSCs are a safe cellular therapy and have great potential to become a viable treatment for neural disorders in the years to come.

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1. Introduction

Adult bone marrow (BM) is home to two types of stem cells, the hematopoietic stem cell (HSC) and the mesenchymal stem cell (MSC). Both types are of mesodermal origin and differentiate into many different cell types along their respective lineage. HSCs have long been studied in the generation of blood and immune cells, while MSCs have been considered relatively insignificant supportive cells for the BM microenvironment (1). However, recently MSCs have become the focus of regenerative medicine and cellular therapeutics. They show immense plasticity with the potential to generate cell types outside mesodermal lineages (2), and typically differentiate into osteocytes, chondrocytes, adipocytes and hematopoietic-supporting stroma (3). With the discovery that MSCs can generate cells of ectodermal and endodermal lineages, they have been allocated as pluripotent rather than just multipotent stem cells due to their broad differentiation capacity (4,5).

It has been proposed that cell replacement therapy will be a likely treatment for neurodegenerative diseases, spinal cord injury and traumatic brain injury in the years to come (6). The degeneration or dysfunction of certain neuronal cell types is observed in these disorders, which would ideally be treated by cell transplantation therapy to replace the damaged cells. Existing research has focused on obtaining the appropriate cell source. In the midst of current research demonstrating the multiple problems with embryonic stem cells (ESCs), such as teratoma formation and expansion issues with the lineage bias of neural stem cells (NSCs), researchers have turned to other adult stem cells (7). Of these, MSCs have the most potential for regenerative medicine (5,8-11). While their plasticity highlights their potential for cellular therapy, MSCs have many other characteristics that make them very attractive for use in cellular treatments. A simple bone marrow aspirate contains approximately 0.0001-0.01% MSCs, but these can easily be isolated and expanded 10^6-fold in culture, thus providing the large numbers required for cell transplantation (12). In addition, MSCs have a low potential to form tumors (3). Another of their unique characteristics is their immunosuppressive property, which allows them to be transplanted across allogeneic barriers (13). They also synthesize and secrete a variety of bioactive factors enabling MSCs with trophic activity, which participates in the structuring of a regenerative microenvironment (9). In fact, MSCs secrete neurotrophic factors

Table I. Selected studies on the types of neural cells derived from mesenchymal stem cells.

Cell source	Type of neural cell generated	Applicability	Refs.
Human adult BM-derived MSCs	Dopaminergic neurons	Parkinson's disease	(21,48)
	Peptidergic neurons	Traumatic nerve injury	(16,17)
Rat BM-derived MSCs	Myelinating Schwann cells	Multiple sclerosis, traumatic nerve injury	(35,65)
	GABAergic and glutaminergic neurons	Traumatic nerve injury, neurodegeneration	(19)
	Photoreceptor cells, retinal neurons	Retinal degeneration	(82)
Mouse BM-derived MSCs	Cholinergic neurons	Alzheimer's disease	(60)

and have demonstrated an inherent ability to promote neural regeneration (14,15). Thus, not only could they be extrapolated as a cell replacement source due to their broad differentiation capacity, they could also be employed for their neurotrophic or 'nutritional' potential.

2. Neural repair by mesenchymal stem cells

Several studies have demonstrated that MSCs can generate cells of neuroectodermal origin (16-21) (Table I). This generation of ectodermal neurons is termed transdifferentiation, or plasticity. Although the plasticity of MSCs is still controversial, many more studies are confirming that they can transdifferentiate or 'jump germ layers' (2). Under various culture conditions and stimulation with inductive factors, MSCs exhibit vast plasticity and are capable of generating several cell types outside of their mesodermal origin. This pluripotent potential might be explained by the similarities they share with ESCs (14,22). The field of MSC transdifferentiation to nerve cells has attracted much attention, as MSCs might become an important cell source for cell therapy in neurodegenerative disorders and traumatic injuries to the nervous system. Initial studies in this field used chemical agents, such as dimethylsulfoxide, isobutylmethylxanthine and ß-mercaptoethanol, to induce the neural transdifferentiation of MSCs (23), but later studies revealed that changes in cell morphology were due to cytotoxicity (24). These studies raised the question of whether MSC transdifferentiation was just an artifact. However, many other studies using reagents such as retinoic acid, basic fibroblast growth factor (bFGF), nerve growth factor (NGF), brain-derived growth factor (BDNF), sonic hedgehog (SHH) and other inductive factors have shown that MSCs can indeed generate functional neuronal cells (16-18,20,25).

The question of whether the cells transdifferentiate *in vivo* or secrete neurotrophic factors to support damaged neurons is still under investigation; finding the answer will require further research. However, we speculate that it could be a mixture of both, and might be dependent on the diseased microenvironment. It is well established that MSCs secrete a wide array of trophic factors that support a regenerative microenvironment (9), including immunomodulatory factors as well as molecules that provide nutritional value to aid in regeneration and injury healing. Regardless of the mechanism, the transplantation of undifferentiated MSCs has shown promise for central nervous system (CNS) disorders (26) (Fig. 1).

3. Multiple sclerosis

Multiple sclerosis (MS) is a degenerative and inflammatory disease of the CNS characterized by sclerotic plaques of the neuronal myelin sheath of the brain and spinal cord due to abnormal fibrosis (27). The disease manifests mostly in young adults, with a clear gender bias towards females. The clinical course depends on the severity of the disease, although most patients develop significant functional impairment in the form of paralysis, sensory and cognitive disturbances, spasticity, tremors, lack of coordination and visual impairment 15-30 years after onset (28). In 85% of patients, MS presents as a relapsing-remitting form, demonstrating episodic relapses of neurological impairment followed by remissions that may be partial or complete (28). Relapsing-remitting MS may develop into secondary progressive disease due to recurrent bouts of inflammation and damage to the CNS in the absence of remission (28,29). The primary-progressive subtype is characterized by a gradual deterioration that is apparent from the onset of the disease (29).

This demyelinating disease has been reported to have an autoimmune etiology, but environmental factors and specific genetic predispositions have also been associated with its progression (30,31). Both CD4^{+} and CD8^{+} T-cells have been found in the acute lesions of MS, with CD4^{+} T-cells being responsible for initiating the event and CD8^{+} T-cells for mediating the amplification and damage of the lesion (32). Its pathogenesis is characterized by the initial breakdown of the blood brain barrier, which has been shown to be achieved by T-cells not specific to the myelin sheath of neurons (30). This breakdown, in turn, enables the entrance of autoreactive T-cells and monocytes into the CNS, causing the destruction of oligodendrocytes, the myelin sheath and axons (30,31). Although this premise is widely accepted, there have also been reports of early MS lesions in the absence of lymphocytes or myelin phagocytosis, with damage due to primary oligodendrocyte apoptosis (32,33). Various theories regarding the initiation events have been proposed, all suggesting that lesions of the CNS are characterized by focal inflammatory reactions involving the death of axons. Most of the proposed theories concerning the pathogenesis of MS stem from experimental allergic/autoimmune encephalomyelitis (EAE) animal models, as it is possible to stimulate the clinical and pathological hallmarks of the disease in them.

The pathogenetic complexity of MS makes the approach to treatment a challenging endeavor. The variability of disease
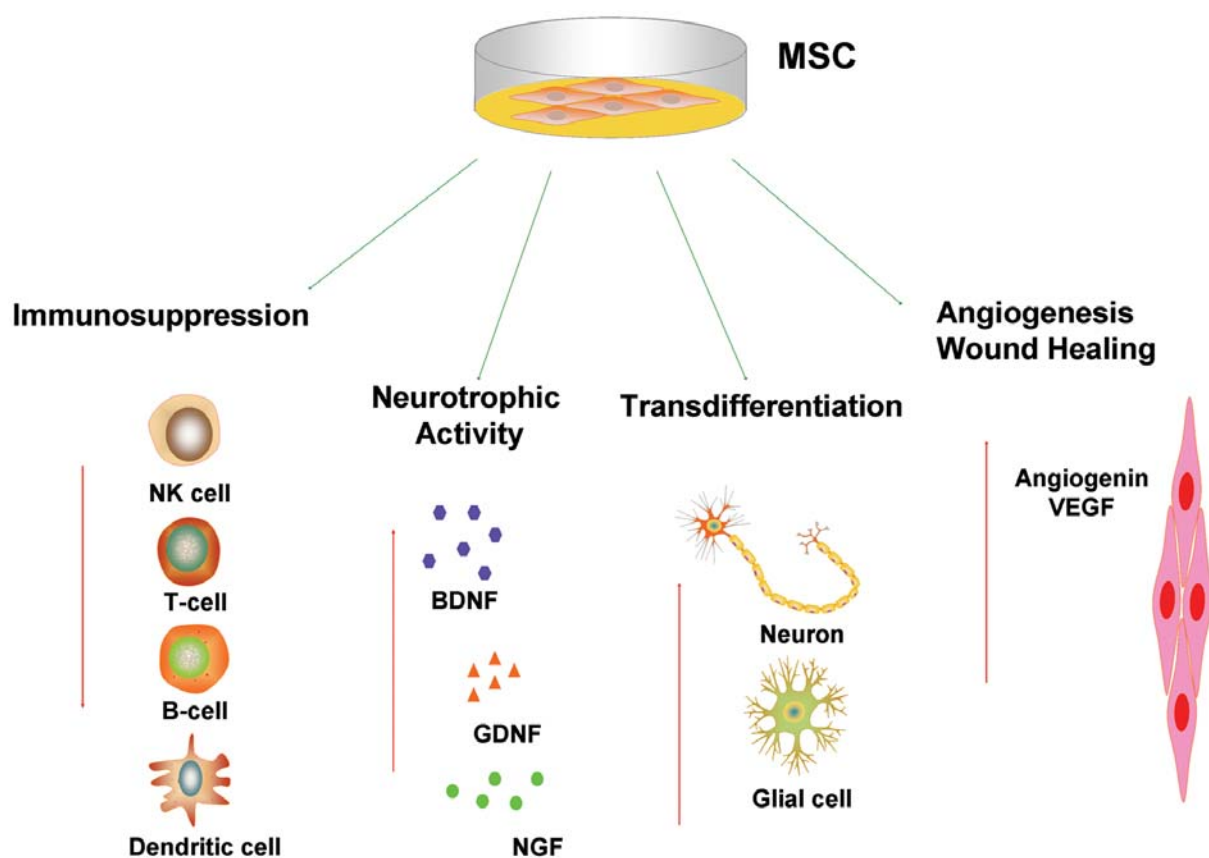
Figure 1. Schematic diagram of the mechanisms by which MSCs may promote neural regeneration and repair. Due to their immunomodulatory properties, MSCs can be immunosuppressive and can provide benefits in cases of multiple sclerosis, an autoimmune disorder. Their neurotrophic effects, or 'nutritional value', and transdifferentiation capabilities are invaluable for all types of neural disorders in which neurons could be rescued or replaced. Additionally, in cases of traumatic nerve injury or stroke, the angiogenic properties of MSCs have proven to be beneficial in providing functional benefit.

manifestation and response to therapies between individuals requires implementation of novel strategies for both immune modulation and neuroprotection. The unique immune regulatory properties and plastic nature of MSCs make them promising candidates in the treatment of MS (11,13,34). Adult MSCs have been shown to transdifferentiate into cells capable of remyelinating the unmyelinated cell line PC12 *in vitro* (35). They have also proved useful in inducing the proliferation of oligodendrocyte precursors by the production of BDNF (36). Zappia *et al* demonstrated that murine MSCs administered to EAE-induced mice resulted in the amelioration of the disease by the suppression of effector T-cells when administered before and during disease onset, including during the peak time period of the disease (37). Moreover, Gerdoni *et al* showed that the injection of MSCs into EAE-induced mice resulted in a milder form of the disease as compared to control mice, due to a decrease in the production of tumor necrosis factor α (TNFα) and interferon γ (IFNγ) (38).

The safety and efficacy shown by MSCs in their use with animal models has allowed for their transition to clinical trials in patients with MS. Mohyeddin Bonab *et al* performed a pilot study using autologous MSCs in 10 patients with progressive MS who did not respond to Mitotraxone treatment (39). Of the 10 patients, six showed some improvement in their degree of sensory, pyramidal and cerebellar functions (39). Another study, conducted by Karrussis *et al*, involved intrathecal and intravenous administration of autologous MSCs

in a 67-year-old female with MS (40). Significant improvement in function was noted 10 months following MSC treatment (40). Promising results with the use of MSCs in these studies open up new perspectives in the treatment of MS.

4. Parkinson's disease

Parkinson's disease (PD) is a neurological movement disorder characterized by rigidity, bradykinesia and tremors. Pathologically, patients show progressive degeneration of dopamine (DA) neurons in the nigrostriatal system of the brain, with ~80% degeneration by the time motor systems become evident (41). Pharmacological agents, such as L-DOPA, are effective in the early stages of the disease, but patients develop severe side effects which significantly impair their quality of life. At the heart of PD is the selective degeneration of DA neurons, explicitly in the substantia nigra. This makes cellular therapy, in which the damaged cells could be replaced by stem cells, a viable treatment. In fact, clinical trials with the transplantation of fetal DA cells into PD patients provided proof of principle that cellular therapy could work for PD (42,43). However, the limited supply of fetal tissue along with variable outcome impelled scientists and physicians to acquire a different source of cells.

There has been an immense amount of scientific research in the past years on stem cells for PD, especially with ESCs and NSCs (7,44). However, many recent reports have demon-

strated the transdifferentiation of MSCs to DA neurons using various induction protocols and animal models (21,25,45-49). Initial studies began with Jiang *et al* in 2003. The group identified a subpopulation of MSCs, termed mouse multipotent adult progenitor cells (MAPCs), that generated most somatic cell lineages, including neural cells (45). The MAPCs generated 25% of cells expressing dopaminergic markers after induction with sonic hedgehog (SHH), fibroblast growth factor 8 (FGF8) and other neurotrophic factors and chemical reagents (45). An articulate study by Dezawa's research team demonstrated that the transfection of MSCs with Notch intracellular domain followed by stimulation with neurotrophic factors (forskolin, bFGF, ciliary neurotrophic factor) and the addition of glial-derived neurotrophic factor (GDNF) generated 41% of dopamine-producing cells (25). Significant improvement in behavioral recovery was observed in PD rat models after transplantation of the MSC-derived dopaminergic neurons (25). On the other hand, another study with similar methodology reported poor survival in PD rat models after the transplantation of transdifferentiated MSCs (49). Other similar studies have shown that MSCs can indeed generate dopaminergic cells ranging in efficiency from 31-35% (46,50). Conversely, our laboratory studies have shown an efficient 67% generation of dopaminergic cells from human BM-derived MSCs within 12 days of induction with SHH, FGF8 and bFGF (21).

MSCs isolated from Wharton's jelly of human umbilical cord blood generated 12.7% dopaminergic cells using neuronal conditioned media, SHH and FGF8 (47). Even with the low percentage of dopamine cells generated, the studies were characterized by significant functional improvement in PD rat models after transplantation, likely due to the neurotrophic activity of MSCs. Perhaps MSCs derived from the umbilical cord have different properties than bone marrow-derived adult MSCs (51), which would account for the low efficiency of dopamine cells acquired by Fu *et al* (47). Tatard *et al* reported on another subpopulation of MSCs that displayed characteristics similar to ESCs, which they termed marrow-isolated adult multilineage inducible (MIAMI) cells (48). These generated an efficient 62% dopaminergic cells after treatment with several inductive and chemical agents, including SHH, FGF8 and retinoic acid.

The aforementioned studies have demonstrated that MSCs are capable of transdifferentiating into cells of a dopamine phenotype. Additionally, the transplantation of undifferentiated MSCs has been proven beneficial in PD mouse models (52).

It was recently reported that contralaterally engrafted MSCs could migrate through the corpus callosum into the lesioned side of the PD mouse model (52), and was speculated that MSCs respond to chemotactic agents in the lesioned areas to which they migrate, repairing the damaged tissue (52). Undifferentiated MSCs from human umbilical cord matrix transplanted into PD rat models also displayed significant functional improvement (53). The authors suggested that the umbilical cord-derived MSCs vetoed the immune response, limiting secondary damage and allowing neuronal repair. Additionally, the secretion of trophic factors by the MSCs promoted functional recovery by rescuing the damaged dopaminergic neurons (53).

5. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is another progressive neurodegenerative disease caused by the death of motor neurons. Throughout the body, muscles gradually weaken and waste away as upper and lower motor neurons degenerate, eventually leading to paralysis and death (54). Degeneration in ALS is moreover quite rapid, and most patients die due to respiratory failure within 3-5 years (54). Unlike PD, which is a slower degenerative disease and affects a specific area of the brain, ALS presents quite a challenge for cellular therapy because of the distributed cell loss throughout the body and the requirement to properly reinnervate muscle tissue.

Transplantation of wild-type BM cells into irradiated SOD1 transgenic mouse models of ALS demonstrated a delay in disease onset and an increase in life span (55). Minimal neural differentiation was detected, thus the authors concluded that functional improvement was likely due to trophic effects. Another study showed that transplantation of human MSCs into SOD1 ALS mice significantly delayed disease onset and progression, in addition to increasing lifespan (56). The human cells survived more than 20 weeks in the xenogenic model, and were able to migrate into the brain and spinal cord and differentiate into neuroglial cells (56).

Initial clinical studies began in 2003, when Mazzini *et al* took autologous MSCs from seven ALS patients and expanded them in culture (57). The cells were directly transplanted into the spinal cord, and did not result in toxicity or uncontrolled proliferation. Three months after transplantation, four patients experienced a mild reduction in muscle strength decline in the lower limbs. In a long term follow-up of the patients, the same group reported, after 36 months, that four of the seven patients showed a significant reduction in the linear decline of lung function and ALS functional rating scale (58). Though these preliminary clinical studies are encouraging, further studies are warranted.

6. Alzheimer's disease

Alzheimer's disease (AD) is another neurodegenerative disease characterized by the progressive impairment of memory and cognitive function, which leads to neuropsychiatric problems, behavioral issues and eventually death. Pathologically, AD patients develop plaques of aggregated amyloid-ß-peptide and neurofibrillary tangles from hyperphosphorylated τ protein (59), resulting in the loss of cholinergic neurons of the basal forebrain and neurons of the adrenergic and serotonergic systems (59). As the disease progresses, there is a widespread degeneration in multiple areas of the brain, including the hippocampus, cerebral cortex and amygdala. The extensive distribution of pathology in the brain of patients makes cellular treatment difficult. However, cell therapy has been suggested as a neuroprotective strategy to delay further degeneration, especially in early stages where neuronal loss is not as extensive and is localized to just the basal forebrain (59).

Research on MSCs and AD is in its infancy. However, a recent study showed positive results in an AD rat model (60). Transplantation of BM-derived MSCs into the hippocampus

of rats injected with ß amyloid protein to mimic AD demonstrated significant improvement based on the Morris Water Maze test (60). The authors suggested that the MSCs transdifferentiated into cholinergic cells and improved the cognitive ability of the AD rat models. These results are promising, but need to be replicated by other researchers if the potential of MSCs in the treatment of AD is to be exploited.

7. Spinal cord injury

Cellular therapy for spinal cord injury (SCI) remains quite challenging. The injury results in a disconnection of long spinal axons leading to severe functional impairment or paralysis. While the distal part of the axon degenerates, the cell body and proximal portion survive, but the axon fails to regenerate. This is mainly due to the formation of a glial scar that secretes axonal growth inhibitory signals and forms a physical barrier separating the injured tissue from normal neuronal tissue (61). Therapeutics have focused either on trophic factor administration to allow axons to re-grow, or on replacing the damaged area with stem cells.

Initial studies investigated the potential of MSCs to migrate and survive in the spinal cord. Satake *et al* documented the migration of rat MSCs through cerebrospinal fluid directly into the lesioned spinal cord in a rat model (62). Immunostaining for nestin revealed that some of the transplanted MSCs transdifferentiated into immature neurons or NSCs. Another study reported on the transplantation of human MSCs into a rat spinal cord injury model (63), following which the immunosuppressed rat models showed significant functional recovery and allowing numerous axons to be identified at the lesion site (63). MSCs were still detected after two weeks from transplantation; however, very few remained after eleven weeks. Similarly, Cizkova *et al* harvested MSCs from human BM donors, expanded them in culture, and injected them intravenously into rat models (64). Interestingly, immunosuppressive drugs were not administered and the human donor MSCs survived in the xenogenic model until the endpoint of the study. MSCs were able to migrate to the spinal cord lesion site and provided significant functional recovery. A small percentage of MSCs differentiated into oligodendrocytes, thereby facilitating recovery by myelinating white matter tracts. However, the majority of cells remained undifferentiated, indicating that the functional recovery observed may have been mediated by the neurotrophic activity of the MSCs. The authors suggest that the incorporation of human MSCs into the rat model and their survival was likely due to their immunomodulatory nature (64).

Transdifferentiation of MSCs into Schwann cells, glial cells that express neurotrophic factors and support axonal growth, has been reported (65). Kamada *et al* induced MSCs into Schwann cells *in vitro* and subsequently grafted them into the spinal cord lesion in rat models. The percentage of neurons was greatly increased, and significant recovery was observed in the hind limbs of the rats (65). Another research group used a bioengineering approach and implanted rat MSCs with macroporous polymer hydrogels to prevent scarring and to bridge the injured cavity of the rat lesioned spinal cord (66). The hydrogels were biocompatible, providing enhanced tissue growth and bridging of the spinal cord lesion. Axonal ingrowth into the hydrogel was also observed. This method provides an efficient alternative to the injection of dissociated cells, consequently maintaining the cells at the injured site and benefiting from cell-matrix interactions that are necessary for regeneration (66).

Further studies demonstrated the use of MSCs in primate models of spinal cord injury (67). MSCs were obtained from rhesus monkeys, transdifferentiated in culture and labeled with a fluorescent dye. The cells were injected directly into the lesioned sites and, after 3 months, the monkeys acquired nearly normal sensory responses. Interestingly, it was thought that the injured microenvironment does not favor neurogenesis, but the implanted MSCs exhibited further *in vivo* differentiation and the monkeys exhibited improved functional recovery (67).

On the basis of positive animal studies, Moviglia *et al* established a human clinical trial with two chronic spinal cord injury patients (68). The group obtained autoimmune T-cells (ATs) and MSCs from two patients, and used the ATs to transdifferentiate the MSCs to NSCs in a coculture method. ATs produce stimulatory cytokines, which can induce transdifferentiation of MSCs to neural cells as well as secreting anti-myelin factors (68). The authors intravenously infused the ATs and injected the MSC-derived NSCs directly into the lesion site. Both patients experienced a progressive improvement during their neuro-rehabilitation program after transplantation. No adverse effects were observed, and the patients acquired a significant level of important sensitivity and motor level recovery (68).

8. Cerebral ischemia/stroke

Cerebral ischemia, or stroke, is a condition in which the brain does not receive enough blood flow and, consequently, lacks oxygenation. This is caused by blockage or obstruction of the contributing blood vessels in the brain, which results in severe brain damage and sometimes death. Depending on the nature of the condition, many different neural cell types or glial cells could be affected, thus making effective cell therapy more difficult. Scientists are actively searching for novel treatments to reduce initial trauma to the brain, and to repair the damage that occurs as a result of the pathological cascade of events after the acute trauma. MSCs could provide functional benefit and reduce ischemic damage through their neurotrophic activity and their ability to transdifferentiate to neural or glial cells (69).

Original studies in this field were established by Li, Chopp and their research team, in which MSCs were transplanted into a mouse stroke model (70). A small proportion of transplanted MSCs were found to express the neuronal nuclei-specific protein NeuN and the glial-specific protein GFAP, indicating transdifferentiation of the MSCs. Additionally, functional recovery was observed in the mouse stroke models, motivating further research on MSCs for the treatment of stroke (70). Chen *et al* later investigated possible mechanisms by which MSCs promote neurological recovery in stroke models (71), demonstrating that MSCs promote endogenous cell proliferation, decrease apoptosis and increase bFGF expression levels, therefore facilitating functional recovery (71). Further experimental studies showed that intracarotid

transplantation of MSCs induced axon and myelin remodeling after stroke (72). MSC therapy increased vessel sprouting, synaptophysin expression and oligodendrocyte precursor cells, indicating that MSCs promote axonal sprouting and remyelination (72). In fact, the beneficial effects of MSC transplantation persisted for at least one year in rat stroke models, with the majority surviving in the brain. Very few were found in the heart, lung, liver, spleen and kidney (73).

The importance of neurotrophic factors was demonstrated in a study in which MSCs were transfected with either BDNF, GDNF, CNTF or NT3 and injected into rat stroke models (69). Rats that received MSCs transfected with either BDNF or GNDF showed reduced damage and improved function, whereas those that received MSCs transfected with CNTF or NT3 failed to show any positive effects. A recent study demonstrated the effects of human MSCs and angiopoietin-overexpressing MSCs in xenogenic rat models of ischemia (74). Intravenous infusion of either MSCs or angiopoietin-modified MSCs resulted in reduced infarction damage, induction of angiogenesis and functional improvement (74). However, MSCs overexpressing angiopoietin showed enhanced angiogenesis at the lesion. Several studies have shown that the infusion of MSCs after a stroke results in a beneficial outcome, due primarily to neurotrophic activity and angiogenesis, which may prove very useful in clinical studies.

9. Traumatic brain injury

Traumatic brain injury (TBI) occurs when there is sudden trauma to the head resulting in brain damage. This could occur as the result of something piercing the brain, or because the head has been violently struck. Disabilities in TBI patients usually depend on the severity and location of the brain damage. Similar to stroke patients, most TBI patients are in need of surgery to repair blocked or obstructed blood vessels. However, in more severe cases patients can be unresponsive or in a coma. As is the case with SCI and stroke, MSCs could repair neural damage through the secretion of cytokines and neurotrophic factors, or by their transdifferentiation ability.

Similar to their studies with stroke, Mahmood *et al* used several approaches to test MSC transplantation as a potential cell therapy for TBI in rat models (75-78). They cultured MSCs with neurotrophic factors BDNF or NGF and transplanted them intracerebrally, injecting MSCs intravenously and transplanting them at different doses. In every case and with every method of transplantation, functional recovery was observed along with the neural transdifferentiation of MSCs (75-78). The studies also demonstrated the importance of BDNF and NGF in the injured brain, as those MSCs cultured prior to transplantation with either neurotrophic factor engrafted in higher numbers (78). Additionally, the expression levels of both BDNF and NGF increased following the intravenous administration of MSCs (75). Recently, this same research group showed that the combined administration of MSCs with statins (atorvastatin) after TBI in rat models augments MSC survival and access to the injured brain (77). Functional improvement was also enhanced in comparison to transplantation of MSCs alone (77). Hu's research group injected MSCs intracisternally into TBI rat models and observed upregulated local gene expression of BDNF and NGF, along

with an improvement in neurological function (79,80). Based on these reports, MSCs along with BDNF and NGF may provide a potential therapeutic application for TBI.

10. Retinitis pigmentosa

Retinitis pigmentosa (RP) is an inherited progressive disorder which results in degeneration of photoreceptor cells, rods and cones in the retina of the eye. Secondary to the degeneration of photoreceptor cells is the slow progression of visual loss (81). Patients initially experience a loss of rod-mediated night vision, and progressively lose total visual ability as cone-mediated central vision is lost (81). Unfortunately, there is no treatment available for patients with RP, but many studies have shown that cell transplantation may be a viable therapy by providing neuroprotective value.

Initial studies began with partial differentiation of MSCs into photoreceptor cells and subsequent transplantation into rat models of retinal degeneration (82). Two weeks following injection, MSCs integrated into the host retina and formed a layer comparable to the normal photoreceptor layer (82). Arnhold and colleagues later investigated whether MSCs could rescue visual effects in mouse models of RP (83). MSCs not only integrated into the retinal pigment epithelium, but also demonstrated neuronal and glial morphologies. The authors also observed noteworthy rescue effects, indicated by the detection of preserved photoreceptor cells (83). Lund *et al* showed that MSCs significantly decreased functional deterioration in rat models of retinal deterioration (84). Trophic factor-secreting ability in the repair of retinal degeneration was tested by Inoue *et al* (85). The researchers found that MSCs promoted photoreceptor survival *in vitro* and delayed retinal degeneration, while preserving retinal function *in vivo* (85). This is very promising, and clinical studies are warranted to confirm the potential of MSCs for patients with RP.

11. Neurometabolic disease

Metachromatic leukodystrophy is a genetic disorder caused by a deficiency in the enzyme arylsulfatase A that results in the accumulation of sulfatides, causing demyelination of the central and peripheral nervous systems (86). In the other neurometabolic disease, Hurler syndrome, patients have a deficiency of α-L-iduronidase enzyme, which results in the accumulation of heparin and dermatan sulfates in lysosomes (86). In most lysosomal storage disorders, the nervous system is predominantly affected and patients develop severe neurological and musculoskeletal deficits. MSCs have been shown to produce high amounts of metabolic enzymes and, because of their differentiation ability and trophic capacity, could repair the damaged tissues.

Research in the field is still in its infancy. However, recent studies have shown that enzymes which are often defective in neurometabolic diseases are biochemically active in MSCs (87). MSCs were found to secrete significant amounts of arylsulfatase A, the enzyme deficient in metachromatic leukodystrophy (87). In addition, coculture experiments demonstrated that fibroblasts from diseased patients were able to uptake the enzyme released into the media by the MSCs. A clinical study testing the transplantation of allogeneic MSCs

Table II. Human clinical trials using mesenchymal stem cells for neurological disease.

Pathological condition	Cellular source	Treatment	Outcome	Refs.
Multiple sclerosis	Autologous BM-derived MSCs	Intrathecal injection of culture expanded MSCs	Improvement in the degree of sensory, pyramidal and cerebellar function	(39)
Amyotrophic lateral sclerosis	Autologous BM-derived MSCs	Transplantation of culture expanded MSCs into the spinal cord	Mild reduction in muscle strength decline, significant reduction in linear decline of lung function	(57,58)
Chronic spinal cord injury	Autologous BM-derived MSCs cocultured with autoimmune T-cells and transdifferentiated to NSCs	I.V. infusion of anti-myelin autoimmune T-cells and infusion of MSC-derived NSCs at the lesion site	Important sensitivity and significant motor level recovery in both patients; no adverse effects observed	(68)
Neurometabolic disease	Allogeneic BM-derived MSCs	I.V. infusion of MSCs	Nerve conduction improved, but no significant clinical change observed; no toxicity reported	(86)

in patients with either Hurler syndrome or metachromatic leukodystrophy showed no toxicity and an improvement in nerve conduction, with slight changes in bone density (86). However, there were no apparent clinical changes observed in the patients. Nevertheless, the authors concluded that the treatment was safe and should be further evaluated as a therapy for neurometabolic diseases.

12. Microenvironmental implications

Although MSCs may seem promising for future therapies of neuronal diseases and disorders, the influence of cytokines and chemokines on the fate of these cells must not be disregarded. MSCs are known to produce cytokines and express receptors for inflammatory mediators (13,88,89). More importantly, they have been shown to respond to low levels of the proinflammatory cytokine IFNγ, resulting in an upregulation of MHC-II and enhancement of their APC properties (34). In contrast, at high levels of IFNγ MHC-II expression is reduced, making MSCs incapable of presenting the antigen (34). This is significant since the therapeutic use of MSCs may involve transplantation within an inflammatory microenvironment. This has a fundamental implication for the use of MSCs in regenerative medicine, specifically neural repair (90). For example, if MSC-derived neurons are implanted in an allogeneic host with spinal cord injury and the host encounters an infection, they may have the potential to revert back to their APC function by re-expressing MHC-II (90). This could lead to an immune response within the host and potential rejection. Therefore, an understanding of these mechanisms is necessary in order to develop various strategies to control their immune properties.

MSCs appear to be preconditioned by microenvironmental factors that allow them to respond to soluble mediators (91). Their pluripotent nature allows for differentiation into various cell types depending on the microenvironment (17,44,92). Consequently, functional crosstalk between MSCs and the microenvironment is highly probable in cases where inflam-

matory mediators are expected to be in areas of tissue injury. This has clinical implications regarding the use of transdifferentiated MSCs and the appropriate stage of development for implantation within injured tissue (89). Depending on the microenvironment, changes within the cell may occur causing oncogenesis, cell death, enhanced immune properties or, in the case of neurons, dysfunctional neurotransmitter synthesis. This could lead to setbacks in stem cell therapy due to detrimental consequences to the patient. Therefore, an understanding of microenvironmental influences on MSCs is integral for successful therapeutic use of these cells.

13. Future prospects

The aforementioned studies substantiate the importance of MSCs in the treatment of neurodegenerative diseases and traumatic injuries of the CNS. It is clear that MSCs play a role in the regeneration and repair of the nervous system by mechanisms including immunosuppression, neurotrophic activity, transdifferentiation and angiogenesis/wound healing (Fig. 1). While many studies have shown the benefit of MSCs in animal models of neurological disease, we will only learn the true potential of these stem cells through patient-based research, which has already begun (Table II). These clinical studies form the impetus for MSCs to transition from bench to bedside.

Acknowledgements

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