

Published in final edited form as:

Neurosci Lett. 2009 June 12; 456(3): 120–123. doi:10.1016/j.neulet.2008.03.096.

Marrow stromal cell transplantation in stroke and traumatic brain injury

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Abstract

There is a paucity of therapies for most central nervous system (CNS) disorders. Bone marrow stromal cells (MSCs) are a mixed cell population, including stem and progenitor cells, and are currently a strong candidate for cell-based therapy in “brain attack”, including stroke, and traumatic brain injury (TBI), since they are easily isolated and can be expanded in culture from patients without ethical and technical problems. Although it has been suggested that trans-differentiation of MSCs into cells of neural lineage may occur *in vitro*, no one has yet observed that MSCs give rise to fully differentiated and functional neurons *in vivo*. The overwhelming body of data indicate that bioactive factors secreted by MSCs in response to the local environment underlie the tissue restorative effects of MSCs. The MSCs that are employed in this therapy are not necessarily stem cells, but progenitor and differentiated cells that escape immune system surveillance and survive in the CNS even for transplantation of allogeneic or xenogeneic MSCs. The injured CNS is stimulated by the MSCs to amplify its intrinsic restorative processes. Treatment of damaged brain with MSCs promotes functional recovery, and facilitates CNS endogenous plasticity and remodeling. The current mini-review is mainly based on our data and focuses on possible cellular and molecular mechanisms of interaction of MSCs with glia, neurons and vessels after brain attack. The transplantation of MSCs opens up new avenues of cell therapy and may provide an effective treatment for various CNS diseases.

Keywords

Bone marrow stromal cells; Stroke; TBI

Stroke and TBI are leading causes of disability worldwide. Following brain attack, a complex and dynamic interaction of neurons, glia and vascular cells determines the extent of the ensuing lesion. The response to CNS insults is a multicellular process that changes continually over time and is regulated by a multitude of extracellular and intracellular molecular signaling events. The adult mammalian CNS is a highly inhibitory environment for axonal regeneration, which severely limits functional recovery after brain damage. There is a compelling need to develop new therapeutic approaches to enhance neurological function after CNS injury. Thus far, treatments post-brain attack have taken essentially two paths, pharmacological and cellular therapies. Pharmacotherapy trials have been performed one drug at a time, often with a single purported mechanism of action. In this manuscript, we focus on cell-based therapy approaches, primarily bone marrow derived stromal cells (MSCs).

Cell therapy can be categorized by their embryonic, fetal or adult origin, and the later two can be further identified by their tissue of origin. MSCs, a mixed cell population including stem, progenitor cells, are also sometimes referred to as mesenchymal stem cells; however, this term should be reserved for a subset of these cells that demonstrate stem cell activity by clearly stated criteria [16]. Potential advantages of MSCs over other types of transplanted cells (e.g., umbilical cord blood, mobilized peripheral blood, and neural stem/progenitor cells) are reviewed by Parr et al. [36], MSCs are easily obtained, available for autologous transplantation, rapidly expanded ex vivo, immune privileged for allogeneic cells, and they migrate to areas of inflammation. Using models of middle cerebral artery occlusion (MCAo) and contusion TBI in rats and mice, we have demonstrated that MSCs derived from donor rats [6,23,30,32], mice [11,25,49] or humans [22] transplanted into rodent brain intracerebrally [25,32], intraarterially [23,29,42], intracisternally [49], intrathecally or intravenously (IV) [6,11,30], significantly improve neurological outcome. We have performed therapeutic window experiments (i.e., 1 day, 1 week, and 1 month) for MSC treatment of temporal or permanent MCAo in young adult, retired breeder and aged rats and animals were sacrificed from 1 month to 1 year after MSC treatment [6,22,30,31,42,43]. Therapeutic benefits are dependent on cellular dose and route, therapeutic window, and animal age [5,6,22,24,42,43]. MSCs survive and selectively target damaged brain tissue in all MSC treated rats and mice. Our data provide evidence that the migration of MSCs are dependent on the specific signals present in the local microenvironment of the damaged brain tissue, e.g., via stromal-derived factor-1 (SDF-1, a chemokine) expressed in astrocytes, neurons and endothelial cells and CXCR4 (receptor of SDF-1) expressed in MSCs [11,43]. Allogeneic and syngeneic MSC treatment after stroke shows no indication of immunologic sensitization (T cell priming or humoral antibody production) in adult rat brain [22,26]. MSCs are not rejected by the host and immunosuppression is not needed in rodents. Treatment of stroke within a range of MSC doses is safe and effective. The feasibility and safety of bone marrow derived cells have been extensively tested and demonstrated in our and other preclinical studies and in clinical trials of many diseases [17,19,46], including stroke [2].

Our studies provide insight into the cellular and molecular mechanisms of MSC interaction with parenchymal cells underlying the therapeutic benefit of MSC treatment of brain attack. Although some MSCs (<10%, depending on the injection route, MSC dose, MSC administration time post-ischemia and sacrifice time post-treatment) co-localized with markers of neural cells, little or no, benefit is derived by replacement of functional neurons with trans-differentiated MSCs *in vivo*. Ultrastructural and electrophysiological analyses have not found neuronal trans-differentiation of MSCs by the presence of specific synapses, or typical neuronal action potentials. MSCs support the growth and differentiation of hematopoietic stem cells. A growing list of evidence suggests that the damaged brain environment promotes a responsive secretion of an array of neurotrophins and bioactive factors by MSCs after stroke [9] and TBI [8], and parenchymal cells, predominantly reactive astrocytes [12,13] foster neurorestoration. Using microarray assay, we measured the changes of the neurotrophin associated gene expression profile in MSCs cultured in the ischemic brain-conditioned medium [37]. Quantitative RT-PCR and immunocytochemistry validated that the ischemic brain-conditioned medium significantly increased neurotrophic and growth factor genes, compared with the normal brain-conditioned medium, including fibroblast growth factor 2 (bFGF), insulin-like growth factor 1 (IGF1), vascular endothelial growth factor A (VEGF_A), nerve growth factor beta (NGF β), brain-derived neurotrophic factor (BDNF) and epidermal growth factor (EGF). Our results indicate that transplanted MSCs work as “small molecular factories” by secreting neurotrophins, growth factors and other supportive substances after brain attack, which may continually produce therapeutic benefits in the damaged brain [37]. The poly-pharmacies secreted from MSCs are potentially more important than any single factor to stimulate CNS repair. Thereby, MSC transplantation

continually facilitates endogenous neurorestorative mechanisms, which include reduction of apoptotic cell death [4] and promotion glial [24,43], neuronal [24,43] and blood vascular [7] remodeling. These restorative events are not mutually exclusive.

Individual cells within the brain may die either by lethal accident (necrosis) or programmed cell death (apoptosis). All nervous tissue consists of neuronal, glial and vascular cells, and apoptosis of these cells is part of a strategy for survival of the damaged nervous tissue [27]. Using light, fluorescent and three-dimensional-laser scanning confocal microscopy (3D-LSCM) in combination with terminal deoxynucleotidyltransferase (TdT)-mediated dUTP-biotin nick end-labeling (TUNEL), in situ hybridization, and immunohistochemistry, we demonstrated that MSC treated rats compared to control animals significantly decrease apoptotic cells in the ischemic boundary zone [4].

Glial cells mainly consist of astrocytes, oligodendrocytes and microglia. Glial cells are at least 10 times more abundant than neurons. An account of neuronal development is beyond the scope of this manuscript; nevertheless, neuronal plasticity in the adult animal may utilize mechanisms that are active during development [21]. In the adult animal after brain attack, axons may also acquire their potential for outgrowth from neighboring astrocytes and establish contacts with existing circuits in the CNS [33]. An understanding of intrinsic signals, especially those involved in the axonal outgrowth bioactive factors that govern the activities (both positive and negative) are needed to develop effective MSC-based treatments for the restoration of function in adults.

With their finely branched processes contacting all parts of neurons (i.e., soma, dendrites, axons, and synapse terminals), and approximately 99% of the brain capillary surface area [18], astrocytes provide many supportive activities essential for neuronal function under physiological circumstances, which include homeostatic maintenance and provision of metabolic substrates for neurons, and the sculpting and maintenance of synapses [45]. Astrocytes are coupled to one another in a cellular network (homo-cellular and heterocellular junctions) via gap junction intercellular communication (GJIC), i.e., by channels composed primarily of connexin43 (Cx43), which is an astrocyte specific functional protein in brain [39]. Previous work in our laboratory suggests that MSCs increase the expression of various neurotrophic or growth factors as well as the GJIC protein Cx43 in astrocytes [12,48]. Astrocytes become “reactive” in response to all CNS insults [45]. Astrocytes promote or inhibit axonal regeneration [45]. Rapidly expanding astrocytic processes create both physical and functional walls surrounding the ischemic core, which extend the time available for marshalling endogenous repair mechanisms, e.g., redirection of blood flow to still salvageable parts of the brain and redirection of neurite sprouting and synapse formation to build a new circuitry. However, reactive astrocytes can also form scars that inhibit axonal regeneration [45].

Previous work in our laboratory suggests that MSCs significantly decrease apoptotic cells in the ischemic boundary zone [4], especially astrocytes, and increase the astrocytic proliferation post-ischemia [13]. Western blot analysis showed that MSCs activate mitogen-activated protein kinase/extracellular signal regulated kinase (MEK/Erk) and phosphoinositide 3-kinase/threonine protein kinase (PI3K/Akt) pathways in astrocytes post-ischemia, and upregulate total Erk1/2 and Akt. Since astrocytes produce various neurotrophic factors, we performed RT-PCR to investigate the effect of MSCs on astrocytic growth factor gene expression post-ischemia. We observed that BDNF, VEGF and bFGF gene expression was enhanced by astrocytes with MSC coculture [13]. Therefore, most importantly, MSCs reduce apoptosis and concurrently increase the production of restorative factors within parenchymal cells, especially in astrocytes. In the adult mammal, the injured CNS limits axonal regeneration that may be attributed to several factors, including lack of

neurotrophins (e.g., glial cell derived neurotrophic factor, GDNF, an axonal outgrowth promoter) and the presence of growth-inhibitory molecules (e.g., chondroitin sulphate proteoglycans, CSPGs). MSC treatment reduces the glial scar surrounding the ischemic lesion area [24,44] suggesting MSCs also reduce factors that inhibit axonal outgrowth. Our data demonstrate that MSCs increase the expression of the GJIC protein Cx43 in astrocytes [12,48]. Hence, we propose that the syncytium-like astrocytes activated by MSCs is a principal mediator of functional recovery post-brain attack.

Oligodendrocytes have branching processes that wrap around axons to form segments of myelin sheaths. Oligodendrocyte progenitors in the subventricular zone (SVZ) of the lateral ventricle migrate into corpus callosum, striatum, and fimbria fornix to differentiate into the nonmyelinating NG2-positive (precursor cells) and mature myelinating oligodendrocytes [35]. Brain injury also induces oligodendrogenesis and newly generated oligodendrocytes participate in myelin repair [3,14,34]. In MSC-treated rats, the number of proliferating cells and oligodendrocyte precursor cells in the ipsilateral hemisphere significantly increased in concert with the enhancement of white matter areas in both hemispheres [24,26,44]. These results suggest that MSCs facilitate axonal sprouting and remyelination in the cortical ischemic boundary zone and corpus callosum, which may partially underlie neurological functional improvement caused by MSC treatment. However, signaling pathways which mediate MSC-enhanced oligodendrogenesis in injured brain remain largely unknown.

Microglia are specialized CNS phagocytes which remove cellular debris and damaged cells. Our data show that brain tissue repair is a dynamic ongoing process with reactive astrocytes, oligodendrocytes and microglia, persisting after stroke injury. MSC treatment reduced the thickness of the scar wall ($p < 0.05$) and reduced the numbers of microglia/macrophages within the scar wall ($p < 0.01$) [24]. The reduction of microglia/macrophages in the scar wall, suggests a lessening need to remove cellular debris in these less damaged regions compared with non-treated rats. Microglia perform a wide variety of functions, including the synthesis and secretion of a number of cytokines, and play a central role in forming a network of immune competent cells in the CNS, including humoral and cellular immunity. Further studies will expand on the generalized changes in the immunological and inflammatory systems induced by MSCs and to test whether these systems affect recovery.

White matter is composed mainly of myelinated axons and provides nerve tracts that connect one part of the brain to another (e.g., superficial to deep, bilateral hemispheres) and connects the brainstem to the spinal cord. Functional recovery after stroke and TBI requires the reorganization of the neural network in the compromised CNS. Depending on the location or the extent of brain attack, patients may partially recover from functional disability spontaneously with time. After cerebral damage to only part of the motor cortex or the pyramidal tract, motor recovery is mediated by reorganization immediately around the lesion site [27]. If the motor cortex is extensively damaged, an alternative network outside the damaged area either in the ipsilateral hemisphere or contralateral hemisphere [41] or in the spinal cord [40] is recruited to assume neurological function [41]. After different routes of administration, most MSCs survive and localize preferentially to the lesion boundary zone. This tissue is potentially salvageable and multiple processes of cell repair are present. A major observation which has given us insight into the action of this MSC therapy is that MSCs restore white matter and promote axonal outgrowth in the CNS.

In response to MSC treatment in rodents subjected to MCAo, there is a significant increase of white matter bundles and their integrity in the striatum and an increase in the area of the corpus callosum [24,44]. Animals subjected to stroke and treated with MSCs demonstrate obvious axonal restructuring which appears to infiltrate into the ischemic boundary zone in the ipsilateral hemisphere [26]. Increased growth-associated protein 43 (GAP43)-positive

axons show intra-cortical axonal projections arising from the ischemic boundary zone toward the ischemic core of parietal cortices after stroke with MSCs, suggesting neurite outgrowth in the peri-infarct region [24]. The reestablishment of synaptic connections between cerebral neurons and their peripheral targets provide the foundation for functional recovery. Synaptophysin, a marker for synapses, was significantly increased in MSC-treated ischemic brains compared with control untreated brains [42,44,48].

The CST is the principal neuronal pathway from the cerebral cortex to the spinal cord, and controls voluntary movements. The major CST is a crossed pathway with pinpointed topographic projections; the lesion in a cerebral hemisphere leads to a contralateral paralysis. We investigated neuroanatomical reorganization after stroke in rodents, spontaneously and treated with MSCs, in both the brain and the spinal cord [28]. Using an anterograde CST tracing method of DiI (a corticospinal tracer) cortical injection, we have demonstrated that axonal sprouting from the intact CST into the denervated side of the spinal cord is enhanced by administration of MSCs in rats subjected to right side MCAo [28]. With retrograde labeling using a pair of trans-synaptic retrograde PRV-152-EGFP (green-left limb) and PRV-614-mRFP (red-right limb) tracers injected into the limb extensor muscles, the cortical pyramidal neurons were labeled with the GFP-right hemisphere or RFP-left hemisphere, respectively. Compared to normal animals, the number of GFP-positive pyramidal cells was reduced in the lesioned right cortex, while the numbers of double-labeled cells (yellowish) were increased both in the ipsilateral and contralateral hemispheres in the MCAo animals. These observations suggest that MSCs have an extraordinary restorative effect on white matter in the brain and promote extensive axonal outgrowth in the spinal cord that is highly correlated with functional recovery [28].

The adult mammalian brain retains neural stem cells that continually generate new neurons within two restricted regions: the subventricular zone (SVZ) of the lateral ventricle and the dentate gyrus subgranular zone (SGZ) of the hippocampus [1]. Neurogenesis in the adult brain is related to neurological function [20]. Many of these SVZ cells express progenitor like molecular markers, such as nestin, β -tubulin isotype 1(TUJ-1), indicative of the activation of adult cerebral tissue into a progenitor or developmental state after brain injury. The proliferation, migration, and maturation of these cells can be controlled by growth and trophic factors and other signaling molecules [38]. Our data support the hypothesis that MSCs play an important role in the proliferation, migration and differentiation of new neurons from the primary source within the SVZ into the injured areas [4,10,24]. A significant increase in new cells are present in the SVZ after ischemic event and are further enhanced by MSC treatment.

Since neither oxygen nor glucose is stored in appreciable amounts in brain, brain repair requires a continuous supply of each substrate to be delivered by the vasculature. After brain attack, collateral circulation may develop by enlargement of pre-existing anastomotic channels or sprouting of new capillaries from existing vascular cells (angiogenesis) [15]. MSCs have the ability to effectively stimulate angiogenesis [10,49] and increase in total surface area of vessels in the ischemic boundary zone compared with control animals [7], indicating that new blood vessels may have been created to nourish the damaged area. VEGF is the key regulator of vasculogenesis and angiogenesis [15]. When we injected human MSCs into rats subjected to MCAo to catalyze brain plasticity, rat VEGF significantly increased [7], suggesting the human MSCs stimulate the production of endogenous rat VEGF. Our studies also reveal that MSC treatment increases secretion of VEGF by reactive astrocytes [13]. Furthermore, we demonstrate that MSCs mediate angiogenesis and vascular integrity through astrocytes [47].

In summary, the innovation of the MSC therapy is that exogenous MSCs provide therapeutic benefit primarily via parenchymal cells, especially astrocytes, to induce remodeling in the CNS which fosters improvement in neurological function. It is our belief that this work will not only facilitate the clinical application of MSCs for the treatment of stroke, but also shed new light on the neglected function of reactive astrocytes in brain repair. Together, our studies provide support for developing MSC-based new therapeutic approaches for treatment of stroke, TBI and other CNS diseases.

Acknowledgments

The work was supported by NINDS grant PO1 NS23393.

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