

Can Adult Bone Marrow Stem Cells Help Repair The Brain?

The bone marrow contains several different stem cell populations that differentiate into peripheral blood cells, vascular endothelial cells and stromal cells. Recent findings suggest that some adult bone marrow stem cells may cross lineage boundaries, giving rise to epithelial cells of the liver, lung, skin and gastrointestinal tract. Bone marrow cells may also turn into skeletal and cardiac muscle cells and into glia and neurons of the brain. While the mechanisms for this plasticity are unknown, the fact that stem cells can develop into several differentiated cell types has led to the possibility of using bone marrow stem cells for the treatment of neurological disorders. It is this area that I shall review in this article.

The low regenerative capacity of the central nervous system (CNS) has limited the success of neurologists in treating traumatic, infectious, inflammatory and degenerative disorders of the brain. Recently, stem cells have raised hopes for future cell therapy in the CNS. By definition, stem cells are capable of self-renewal and differentiation into at least one mature cell type (Anderson *et al.*, 2001). While embryonic stem cells derived from the inner blastocyst are considered “pluripotent”, i.e. capable of generating all differentiated cell types in the body, adult stem cells have been thought to have a limited differentiative potential. However, several recent studies in rodents and humans suggest that adult stem cells may show far more plasticity than previously assumed (Fig. 1).

Bone marrow stem cells

The postnatal bone marrow (BM) contains several different stem and progenitor cell populations. Hematopoietic stem cells (HSCs) differentiate into all mature blood cell types and are able to reconstitute the hematopoietic system of a myeloablated host (Weissman, 2000). Marrow stromal cells (MSCs) differentiate into nonhematopoietic cells, including osteocytes, chondrocytes and adipocytes (Minguell *et al.*, 2001). Multipotent adult progenitor cells (MAPCs) copurify with MSCs and can be cultured indefinitely (Jiang *et al.*, 2002). Endothelial progenitor cells (EPCs) can be mobilised into the peripheral blood and give rise to mature endothelial cells in vessels (Asahara *et al.*, 1997).

Hematopoietic stem cells (HSCs): When HSCs are transplanted into irradiated recipient mice, hematopoiesis is reconstituted with donor-derived cells within weeks (Spangrude *et al.*, 1995). Moreover, recent

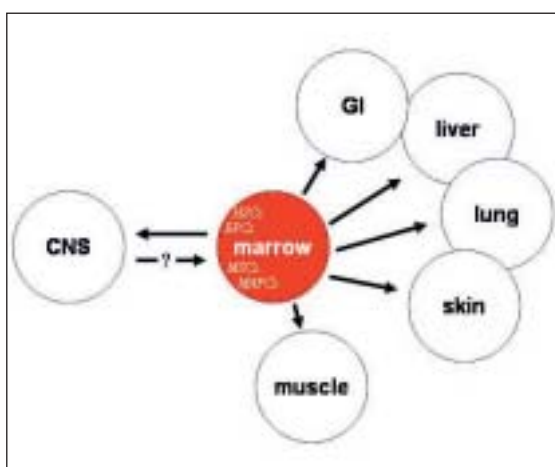


Figure 1. Plasticity of adult bone marrow stem cells. BM stem cells were shown to give rise to hepatocytes, keratinocytes, pneumocytes and epithelial cells in the gastrointestinal tract (GI). BM stem cells were also found to turn into myofibres of the heart and skeletal muscle. In the brain, all glial cell types, endothelia and neurons could be derived from BM stem cells (HSCs: hematopoietic stem cells; EPCs: endothelial progenitor cells; MSCs: mesenchymal stem cells; MAPCs: multipotent adult progenitor cells), while the hematopoietic competence of neural stem cells remains controversial.

findings suggest that up to 20% of the pneumocytes of the lung and 0.5-3% of the epithelial cells of the skin and gastrointestinal tract are derived from the donor cell 11 months after transplantation of a single HSC (Krause *et al.*, 2001). In a subsequent study using transplantation of an HSC marked with the green fluorescent protein (GFP), only hepatocytes in the liver were found to be derived from the donor cell (Wagers *et al.*, 2002). Multipotent adult progenitor cells (MAPCs): MAPCs are a population of BM stem cells that differentiate, at the single cell level, not only into mesenchymal cells, but also into cells with visceral mesoderm, neuroectoderm and endoderm characteristics when injected into an early mouse blastocyst (Jiang *et al.*, 2002). Recently, the transplantation of GFP-expressing BM cells into lethally irradiated mice was found to result in the generation of BM-derived skeletal muscle satellite cells and myofibers (LaBarge and Blau, 2002). Even in human female recipients of male bone marrow transplants, epithelial cells in the liver, skin and gastrointestinal tract were found to contain a Y chromosome indicating donor origin (Theise *et al.*, 2000; Korblyng *et al.*, 2002). Moreover, transplantation of sex-mismatched hearts and kidneys in humans resulted in substantial engraftment of recipient-derived cardiac myocytes and renal epithelial cells in the transplanted organs (Quaini *et al.*, 2002; Poulsom *et al.*, 2001).

From marrow to brain

In contrast to peripheral organs, the brain is a rather secluded site. The blood-brain barrier contains endothelial tight junctions and limits the access of serum constituents and circulating cells to the CNS. Nevertheless, monocytes/macrophages can continuously enter the rodent brain and tend to locate to the perivascular sites or differentiate into parenchymal microglia (Hickey and Kimura, 1988; Kennedy and Abkowitz, 1997; Priller *et al.*, 2001a). Although astrocytes and oligodendrocytes originate from the neuroectoderm, several groups have recently found that BM cells can also give rise to both cell types in the murine brain (Eglitis and Mezey, 1997; Bonilla *et al.*, 2002; Corti *et al.*, 2002). Interestingly, this microglial and astroglial engraftment is significantly enhanced after CNS injury (Eglitis *et al.*, 1999; Flügel *et al.*, 2001; Priller *et al.*, 2001a). Indeed even neurons have been found to express markers of the transplanted bone marrow in chimeric mice (Brazelton *et al.*, 2000; Mezey *et al.*, 2000; Priller *et al.*, 2001b; Corti *et al.*, 2002) and in the cerebellum, fully developed Purkinje cells expressing GFP have been reported after transplantation of GFP-marked BM stem cells (Priller *et al.*, 2001b; Wagers *et al.*, 2002). In human studies, the female recipients of male bone marrow transplants showed that almost 0.1% of the neurons, including Purkinje cells, contained a Y-chromosome several months after BM transplantation (Mezey *et al.*, 2003; Weimann *et al.*, 2003). However, it is becoming clear that most of these cells arose from fusion of the adult stem cells with host neurons (Alvarez-Dolado *et al.*, 2003).



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Table 1. Summary of recent studies demonstrating a clinical benefit from the transplantation of mesenchymal stem cells in rodent models of neurological disorders.

lesion (neurological disorder)	BM cell type	therapeutic benefit	references
cerebral ischemia (<i>stroke</i>)	MSCs	+	Li et al., 2000, 2001a Chen et al., 2001 Zhao et al., 2002
MPTP (<i>Parkinson's disease</i>)	MSCs	+	Li et al., 2001b
TBI, spinal contusion (<i>trauma</i>)	MSCs	+	Mahmood et al., 2001 Hofstetter et al., 2002
spinal cord demyelination (<i>multiple sclerosis</i>)	MSCs	+	Akiyama et al., 2002
acid sphingomyelinase deficiency (<i>Niemann-Pick disease</i>)	MSCs	+	Jin et al., 2002

Therapeutic potential of bone marrow stem cells

The apparent plasticity of BM stem cells has raised hopes for their use in cell-based repair strategies in the CNS. In mouse models of neurological disorders, the transplantation of MSCs has resulted in significant clinical improvement in several studies (Table 1).

- Intravenous, intracarotid and intracerebral administration of MSCs after cerebral ischemia improved behavioural recovery in mice and rats (Li *et al.*, 2000; Li *et al.*, 2001a; Chen *et al.*, 2001; Zhao *et al.*, 2002). Furthermore, bone marrow-derived cells also contributed to neovascularisation after cerebral ischemia in mice (Zhang *et al.*, 2002; Hess *et al.*, 2002).
- In the MPTP (methyl-phenyl-tetrahydropyridine) mouse model of Parkinson's disease, intrastriatal transplantation of MSCs has promoted functional recovery (Li *et al.*, 2001b).
- Rats injected with MSCs after spinal contusion and traumatic brain injury also showed long-term improvement of locomotor function (Mahmood *et al.*, 2001; Hofstetter *et al.*, 2002).
- Finally, MSCs were found to remyelinate the rat spinal cord after focal demyelination and to improve conduction velocity (Akiyama *et al.*, 2002).

The results suggest that BM stem cell transplantation may represent a new avenue for the treatment of neurological disorders. In fact, several clinical trials are already underway trying to determine the efficiency of BM stem cell therapy in neurological diseases, such as multiple sclerosis and stroke. Interestingly, intracerebral transplantation of acid sphingomyelinase (ASM)-expressing MSCs into ASM-deficient mice resulted in a significant delay of Purkinje cell loss in this model of Niemann-Pick disease, and the surviving Purkinje cells contained ASM (Jin *et al.*, 2002). On the other hand, recent experimental evidence suggests that the beneficial effects of BM stem cell administration may result from the supply of trophic factors rather than the differentiation of BM-derived cells into neurons, glia or endothelial cells in the injured brain (Li *et al.*, 2002). While the clinical potential of BM stem cell therapy is apparent, there is much to be learnt about the basic biology of stem cell plasticity before we can fully acknowledge the value of bone marrow stem cells in the brain.

References:

Akiyama Y, Radtke C, Kocsis JD (2002) Remyelination of the rat spinal cord by transplantation of identified bone marrow stromal cells. *J Neurosci* 22:6623-6630.
Anderson DJ, Gage FH, Weissmann IL (2001) Can stem cells cross lineage boundaries? *Nat Med* 7:393-395.
Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T,

Witzenbichler B, Schatteman G, Isner JM (1997) Isolation of putative progenitor endothelial cells for angiogenesis. *Science* 275:964-967.
Bonilla S, Alarcon P, Villaverde R, Aparicio P, Silva A, Martinez S (2002) Haematopoietic progenitor cells from adult bone marrow differentiate into cells that express oligodendroglial antigens in the neonatal-mouse brain. *Eur J Neurosci* 15:575-582.
Brazelton TR, Rossi FM, Keshet GI, Blau HM (2000) From marrow to brain: expression of neuronal phenotypes in adult mice. *Science* 290:1775-1779.
Chen J, Li Y, Wang L, Zhang Z, Lu D, Lu M, Chopp M (2001) Therapeutic benefit of intravenous administration of bone marrow stromal cells after cerebral ischemia in rats. *Stroke* 32:1005-1011.
Corti S, Locatelli F, Strazzer S, Salani S, Del Bo R, Soligo D, Bossolasco P, Bresolin N, Scarlato G, Comi GP (2002) Modulated generation of neuronal cells from bone marrow by expansion and mobilization of circulating stem cells with in vivo cytokine treatment. *Exp Neurol* 177:443-452.
Eglitis MA, Mezey E (1997) Hematopoietic cells differentiate into both microglia and macroglia in the brains of adult mice. *Proc Natl Acad Sci U S A* 94:4080-4085.
Eglitis MA, Dawson D, Park KW, Mouradian MM (1999) Targeting of marrow-derived astrocytes to the ischemic brain. *Neuroreport* 10:1289-1292.
Hess DC, Hill WD, Martin-Studdard A, Carroll J, Brailer J, Carothers J (2002) Bone marrow as a source of endothelial cells and NeuN-expressing cells after stroke. *Stroke* 33:1362-1368.
Hickey WF, Kimura H (1988) Perivascular microglial cells of the CNS are bone marrow-derived and present antigen in vivo. *Science* 239:290-292.
Hofstetter CP, Schwarz EJ, Hess D, Widenfalk J, El Manira A, Prockop DJ, Olson L (2002) Marrow stromal cells form guiding strands in the injured spinal cord and promote recovery. *Proc Natl Acad Sci U S A* 99:2199-2204.
Jiang Y, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, Reyes M, Lenvik T, Lund T, Blackstad M, Du J, Aldrich S, Lisberg A, Low WC, Largaespada DA, Verfaillie CM (2002) Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature* 418:41-49.
Jin HK, Carter JE, Huntley GW, Schuchman EH (2002) Intracerebral transplantation of mesenchymal stem cells into acid sphingomyelinase-deficient mice delays the onset of neurological abnormalities and extends their life span. *J Clin Invest* 109:1183-1191.
Kennedy DW, Abkowitz JL (1997) Kinetics of central nervous system microglial and macrophage engraftment: analysis using a transgenic bone marrow transplantation model. *Blood* 90:986-993.
Korbling M, Katz RL, Khanna A, Ruitfrok AC, Rondon G, Albitar M, Champlin RE, Estrov Z (2002) Hepatocytes and epithelial cells of donor origin in recipients of peripheral-blood stem cells. *N Engl J Med* 346:738-746.
Krause DS, Theise ND, Collector MI, Henegariu O, Hwang S, Gardner R, Neutzel S, Sharkis SJ (2001) Multi-organ, multi-lineage engraftment by a single bone marrow-derived stem cell. *Cell* 105:369-377.
LaBarge MA, Blau HM (2002) Biological progression from adult bone marrow to mononucleate muscle stem cell to multinucleate muscle fiber in response to injury. *Cell* 111:589-601.
Li Y, Chopp M, Chen J, Wang L, Gautam SC, Xu YX, Zhang Z (2000) Intrastriatal transplantation of bone marrow nonhematopoietic cells improves functional recovery after stroke in adult mice. *J Cereb Blood Flow Metab* 20:1311-1319.
Li Y, Chen J, Wang L, Lu M, Chopp M (2001a) Treatment of stroke in rat with intracarotid administration of marrow stromal cells. *Neurology* 56:1666-1672.
Li Y, Chen J, Wang L, Zhang L, Lu M, Chopp M (2001b) Intracerebral transplantation of bone marrow stromal cells in a 1-methyl-4-phenyl-

1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. *Neurosci Lett* 316:67-70.

Li Y, Chen J, Chen XG, Wang L, Gautam SC, Xu YX, Katakowski M, Zhang LJ, Lu M, Janakiraman N, Chopp M (2002) *Human marrow stromal cell therapy for stroke in rat: neurotrophins and functional recovery*. *Neurology* 59:514-523.

Mahmood A, Lu D, Wang L, Li Y, Lu M, Chopp M (2001) *Treatment of traumatic brain injury in female rats with intravenous administration of bone marrow stromal cells*. *Neurosurgery* 49:1196-1203.

Mezey E, Chandross KJ, Harta G, Maki RA, McKercher SR (2000) *Turning blood into brain: cells bearing neuronal antigens generated in vivo from bone marrow*. *Science* 290:1779-1782.

Mezey E, Key S, Vogelsang G, Szalayova I, Lange DG, Cain B (2003) *Transplanted bone marrow generates new neurons in human brains*. *Proc Natl Acad Sci U S A* 100:1364-1369.

Minguell JJ, Erices A, Conget P (2001) *Mesenchymal stem cells*. *Exp Biol Med* 226:507-520.

Poulsom R, Forbes SJ, Hodivala-Dilke K, Ryan E, Wyles S, Navaratnasah S, Jeffrey R, Hunt T, Alison M, Cook T, Pusey C, Wright NA (2001) *Bone marrow contributes to renal parenchymal turnover and regeneration*. *J Pathol* 195:229-235.

Priller J, Flügel A, Wehner T, Boentert M, Haas CA, Prinz M, Fernandez-Klett F, Prass K, Bechmann I, de Boer BA, Frotscher M, Kreutzberg GW, Persons DA, Dirnagl U (2001a) *Targeting gene-modified hematopoietic cells to the central nervous system: use of green fluorescent protein uncovers microglial engraftment*. *Nat Med* 7:1356-1361.

Priller J, Persons DA, Klett FF, Kempermann G, Kreutzberg GW, Dirnagl U (2001b) *Neogenesis of cerebellar Purkinje neurons from gene-marked bone marrow cells in vivo*. *J Cell Biol* 155:733-738.

Quaini F, Urbanek K, Beltrami AP, Finato N, Beltrami CA, Nadel-Ginard B, Kajstura J, Leri A, Anversa P (2002) *Chimerism of the transplanted heart*. *N Engl J Med* 346:5-15.

Spangrude GJ, Brooks DM, Tumas DB (1995) *Long-term repopulation of irradiated mice with limiting numbers of purified hematopoietic stem cells: In vivo expansion of stem cell phenotype but not function*. *Blood* 85:1006-1016.

Theise ND, Nimmakayalu M, Gardner R, Illei PB, Morgan G, Teperman L, Henegariu O, Krause DS (2000) *Liver from bone marrow in humans*. *Hepatology* 32:11-16.

Wagers AJ, Sherwood RI, Christensen JL, Weissman IL (2002) *Little evidence for developmental plasticity of adult hematopoietic stem cells*. *Science* 297:2256-2259.

Weimann JM, Charlton CA, Brazelton TR, Hackman RC, Blau HM (2003) *Contribution of transplanted bone marrow cells to Purkinje neurons in human adult brains*. *Proc Natl Acad Sci U S A* 100:2088-2093.

Weissman IL (2000) *Translating stem and progenitor cell biology to the clinic: barriers and opportunities*. *Science* 287:1442-1446.

Zhang ZG, Zhang L, Jiang Q, Chopp M (2002) *Bone marrow-derived endothelial progenitor cells participate in cerebral neovascularization after focal cerebral ischemia in the adult mouse*. *Circ Res* 90:284-288.

Zhao LR, Duan WM, Reyes M, Keene CD, Verfaillie CM, Low WC (2002) *Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats*. *Exp Neurol* 174:11-20.

Alvarez-Dolado M, Pardal R, Garcia-Verdugo JM, Fike JR, Lee HO, Pfeffer K, Lois C, Morrison SJ, Alvarez-Buylla A (2003) *Fusion of bone-marrow-derived cells with Purkinje neurons, cardiomyocytes and hepatocytes!* *Nature* 425:968-973.

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