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 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; Korbling 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; Poulson 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).
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, intrasratial 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 recovery 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).

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:
Li Y, Chen J, Wang L, Zhang Z, Lu M, Chopp M (2001b) Intracerebral transplantation of bone marrow stromal cells in a 1-methyl-4-phenyl-

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

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<thead>
<tr>
<th>lesion (neurological disorder)</th>
<th>BM cell type</th>
<th>therapeutic benefit</th>
<th>references</th>
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<tr>
<td>cerebral ischemia (stroke)</td>
<td>MSCs</td>
<td>+</td>
<td>Li et al., 2000, 2001a</td>
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<tr>
<td>MPTP (Parkinson’s disease)</td>
<td>MSCs</td>
<td></td>
<td>Chen et al., 2001</td>
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<tr>
<td>TBI, spinal contusion (trauma)</td>
<td>MSCs</td>
<td>+</td>
<td>Zhao et al., 2002</td>
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<tr>
<td>spinal cord demyelination</td>
<td>MSCs</td>
<td>+</td>
<td>Li et al., 2001b</td>
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<tr>
<td>(multiple sclerosis)</td>
<td></td>
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<td>Mahmood et al., 2001</td>
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<tr>
<td>acid sphingomyelinate</td>
<td>MSCs</td>
<td>+</td>
<td>Hofstetter et al., 2002</td>
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<tr>
<td>deficiency (Niemann-Pick disease)</td>
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<td>Akaiyama et al., 2002</td>
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1,2,3,6-tetrahydropyridine mouse model of Parkinson’s disease. 
Li Y, Chen J, Chen XG, Wang L, Gautam SC, Xu YX, Katakowski M, 
stromal cell therapy for stroke in rat: neurotrophins and functional 
of traumatic brain injury in female rats with intravenous administra-
Transplanted bone marrow generates new neurons in human brains.
Poulsom Robertson B, Forbes SL, Hodiivala-Dilke K, Ryan E, Wyles S, 
Navaratnarasah S, Jeffrey R, Hunt T, Alison M, Cook T, Pusey C, 
Wright NA (2001) Bone marrow contributes to renal parenchymal 
Priller J, Flugel A, Wehner T, Boentert M, Haas CA, Prinz M, 
Fernandez-Klett F, Kempermann G, Kreutzberg GW, Persson DA, 
Danrgul U (2001a) Targeting gene-modified hematopoietic cells to the 
Priller J, Persson DA, Moleti KL, Kempermann G, Kreutzberg GW, 
Darngal U (2001b) Neogenesis of cerebellar Purkinje neurons from gene-
Quaini F, Urbanek K, Beltrami AP, Sinnoto N, Beltrami CA, Nadel-
Spangrude GL, Brooks DB, Muns DA (1995) Long-term repopulation of 
Thesis ND, Nimmakayalu M, Gardner R, Iller PB, Morgan G, 
Teperman L, Henegariu O, Krasse DS (2000) Liver from bone marrow in 
Weimann JM, Charlton CA, Braelton TR, Hackman RC, Blau HM 
(2003) Contribution of transplanted bone marrow cells to Purkinje neu-
Weissman IL (2000) Translating stem and progenitor cell biology to the 
Zhao ZG, Zhang L, Jiang Q, Chopp M (2002) Bone marrow-derived 
Priller J, Flugel A, Wehner T, Boentert M, Haas CA, Prinz M, 
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Spangrude GL, Brooks DB, Muns DA (1995) Long-term repopulation of 
Thesis ND, Nimmakayalu M, Gardner R, Iller PB, Morgan G, 
Teperman L, Henegariu O, Krasse DS (2000) Liver from bone marrow in 
Weimann JM, Charlton CA, Braelton TR, Hackman RC, Blau HM 
(2003) Contribution of transplanted bone marrow cells to Purkinje neu-
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