Do Bone Marrow Cells Generate Neurons?

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In the past 5 years, accumulating evidence has demonstrated plasticity of bone marrow–derived cells. Bone marrow–derived cells display the capacity to change their fate, differentiating into hepatocytes, endothelial cells, muscle cells, and cardiomyocytes, and even neurons.1 The findings that bone marrow cells differentiate into neurons in vitro and in vivo challenge previous assumptions that tissue-specific stem cells give rise only to cells of their organ of origin and do not cross lineages.

Bone marrow contains a heterogeneous population of stem and progenitor cells. Two of the best defined are the hematopoietic stem cells and the bone marrow stromal cells or mesenchymal stem cells.1 There have been a number of reports of in vitro differentiation of bone marrow stromal cells into neurons on exposure to various inducing regimens.2 Co-isolating with mesenchymal stem cells is the multipotent adult progenitor cell, a rare cell in the bone marrow that expands and exhibits remarkable plasticity in culture.3 Multipotent adult progenitor cells differentiate into endothelial cells, hepatocytes, and neurons in vitro and, after injection into a blastocyst, differentiate into cells from all germ layers including neurons.3 While originally isolated from bone marrow, multipotent adult progenitor cells have now been cultured from muscle and brain.4 It is not clear, however, whether the multipotent adult progenitor cell is an artifact of cell culture or whether it is a rare multipotent stem cell in vivo.

DIFFERENTIATION OF BONE MARROW CELLS INTO NEURONS: EVIDENCE FROM ANIMAL STUDIES

The common method for determining the fate of bone marrow cells involves transplanting genetically marked bone marrow in mice that have received lethal irradiation. This produces a “radiation chimera,” and the fate of the bone marrow cells is tracked over time by detecting the genetic tag in histologic sections. This tagging is often in the form of sex mismatch, in which male Y chromosome marrow is transplanted into female recipients or in which the donor’s bone marrow is genetically tagged, usually with lacZ or green fluorescent protein (GFP).

Using a radiation chimera model in which adult mice were subjected to lethal irradiation and then transplanted with marrow from mice that ubiquitously expressed GFP, Brazelton and colleagues5 reported, after flow cytometric analysis of the dissociated brain, that 20% of the cells did not express hematopoietic markers. Confocal microscopy demonstrated that individual cells in histologic sections coexpressed GFP and the neuron-specific proteins, NeuN, the 200-kDa isoform of neurofilament (NF-H), or class IIIB tubulin. Individual cells coexpressed not only GFP and NeuN but also pCREB (phosphorylated cyclic adenosine monophosphate–responsive element binding protein), a transcription factor activated by phosphorylation. The olfactory bulb, being an active site of neurogenesis, was selected for quantification; 0.2% to 0.3% of the neurons were bone marrow derived by 8 to 12 weeks after transplantation.

Mezey and colleagues6 transplanted Y chromosome marrow without irradiation...
EVIDENCE OF BONE MARROW–DERIVED NEURONS IN HUMANS?

Sex-mismatched bone marrow transplants in which bone marrow derived from a male donor was transplanted into a female recipient affords an opportunity to track the fate of bone marrow cells in human brain. In 4 females with survival of 2 to 10 months, cells double labeled for Y chromosome and a neuronal marker (either NeuN or Kv2.1, a neuron-specific voltage-gated potassium channel) were noted, mostly in neocortex and hippocampus. Estimates of the number of bone marrow–derived neurons were 0.025% to 0.05% in this short period.

Similar evidence has been found for bone marrow cells contributing to Purkinje cells in human brain. In female patients who received bone marrow transplants from males, 4 Purkinje cells were seen with Y chromosomes, indicating that these were derived from the male bone marrow. A total of 5860 Purkinje cells were examined, of which 4 showed a Y chromosome, indicating that bone marrow contributed to 0.1% of Purkinje cells. Interestingly, 2 Purkinje cells were seen that contained more than a diploid number of sex chromosomes, suggesting that cell fusion had occurred. Since the sections examined were 10 µm thick and a Purkinje cell nucleus is much larger than this, it is highly possible that sex chromosomes distributed in a large nucleus can be missed when thin sections are examined. Two possible mechanisms exist for appearance of bone marrow–derived Purkinje cells: either a change in cell fate or the fusion of bone marrow cells with host Purkinje cells. Since the period after transplantation was so short (3-15 months) and the Y chromosome containing Purkinje cells appeared to have full dendritic branching, cell fusion may be the most plausible mechanism.

FUSION

The first reports that cell fusion might be responsible for the apparent plasticity of bone marrow cells came from

Generation of Purkinje cells from a bone marrow–derived cell may involve
differentiation from bone marrow cell (A) or cell fusion (B).
in vitro studies in which bone marrow cells were cocultured with embryonic stem cells. Terada and colleagues\textsuperscript{14} cultured GFP-expressing bone marrow–derived cells with murine embryonic stem cells and found that, under selective pressure, GFP-expressing cells that developed the characteristics of embryonic stem cells (differentiated into cardiomyocytes in vitro and also formed teratomas after injection into nonobese diabetic–severe combined immune-deficiency mice) had double the amount of DNA, suggesting that the bone marrow cells had fused with the embryonic stem cells. These cell fusion events, however, were rare (1 in 10\textsuperscript{5}), and a population of cells enriched for stem cell antigen 1–positive, lineage-negative cells did not show these hybrid events, making it unlikely that hematopoietic stem cells were involved in these fusion events, but that perhaps a more differentiated bone marrow cell such as a monocyte was involved.

Cell fusion has also been shown in vivo. In a murine model of tyrosinemia type I with mutations in the fumarylacetoacetate hydrolase gene (\textit{Fah}--), transplanted \textit{Fah}+/+ bone marrow cells fused with recipient hepatocytes, expressed a hepatocyte gene profile and the wild-type \textit{Fah} gene, and corrected the metabolic disorder.\textsuperscript{15} This observation demonstrates that these fused cells are functional and serve to rescue impaired recipient cells. However, while cell fusion may indeed account for some of the “plasticity” of bone marrow cells, particularly in the liver, it does not seem to account for all reports of bone marrow “plasticity.”\textsuperscript{11}

**CONCLUSIONS**

There is evidence in mice and humans that bone marrow cells contribute to neurons. However, most of this work has relied on immunocytochemistry, and there is concern over the specificity of the markers used. Still lacking is electrophysiologic evidence that the cells generated in vivo have the functional characteristics of neurons. There is strong evidence in mice and humans that bone marrow cells either fuse with or generate Purkinje cells. Cell fusion itself is a remarkable phenomenon, as evidence from the liver suggests that this mechanism may be important in repair and correction of a metabolic disorder. It is possible that bone marrow cells, either by direct generation or by cell fusion, could play a role in repair of central nervous system damage.

Since the acceptance of this manuscript, additional evidence has been published demonstrating that bone marrow cells fuse with Purkinje cells in the mouse.\textsuperscript{16,17}

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