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Editorial and Views

Transplanting bone-marrow stem cells into the central nervous system

Pluripotent stem cells have been identified *in vivo* in the central nervous system of animals and in tissue cultures, and a number of authors have established that these cells proliferate and differentiate into neurons and glia in the adult nervous system of vertebrates. The pluripotent role of central nervous system stem cells has also been confirmed by their transplantation, with results being similar to those obtained by transplanting fetal cells.[1] However, in adult animal brains less than 3% of the proliferating cells labeled with deoxybromouridine differentiate into neurons. This discrepancy in the efficiency of cell differentiation in culture and *in vivo* probably depends on some little understood signal transduction functions. Identifying the intracellular intracytoplasmic proteins that regulate the differentiation of pluripotent stem cells, as well as the number of stem cells necessary for neuronal transformation, will be fundamental for the future therapy of a number of neurodegenerative diseases.

Although neuron production had been observed in experimental animals of different species 30 years ago, the capacity of neurogenesis in humans was not discovered until 1998, when Eriksson *et al*.[2] transplanted cells collected from the brains of deceased cancer patients and showed that neurons are routinely produced in the adult hippocampus.

In rodents, neurogenesis occurs not only in the hippocampus but also in the olfactory system, but it is not known whether it takes place in areas of the human brain other than the hippocampus.

Given the few stem cells existing in the central nervous system, we need to know the number and location of those that are capable of evolving into neurons in different brains sites, and be sure that these neurons will be functional, and send and receive messages appropriately.

Animal studies have demonstrated that environmental enrichment with certain growth factors such as epidermal growth factor[3] and fibroblast growth factor[4] influence the neurogenesis of pluripotent stem cells.

When embryonic stem cells were transplanted into the brain of mice some of the engrafted cells were transformed into dopaminergic and serotonergic secreting neurons, whereas others synthesized substances in different classes of neurons.[5]

Neurogenesis also seems to occur when bone marrow stromal cells are transplanted into rat brain.[6]

Thomson *et al.*[7] reported that after proliferation *in vitro*, embryonic stem cells from human blastocysts maintained the developmental potential of all three embryonic germ lines including the neural epithelium. If it were possible to control the proliferation and differentiation of embryonic stem cells in culture, and then transplant them in order to induce neurogenesis, this might help to repair the lesions observed in some neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. A double blind study of 40 patients affected by Parkinson's disease conducted by Helmuth *et al*.[8] showed that disease progression was slowed in the 20 patients whose brains were transplanted with fetal cells derived from four 7-8 week old embryos. However, the use of *in vitro* cultured human embryonic stem cells in human diseases is felt to be unjustifiable by many people and raises serious ethical problems, which is why attention was directed towards bone marrow stem cells. One recent study has shown[9] that is possible to modify partially committed stem cells in such a way as to change the course of their development (e.g. using retinoid acid, leukemia inhibitory factor).

Bone marrow stem cells develop into mesenchymal and hemopoietic lineage cells. Mesenchymal stem cells have multilineage potential, contributing towards the regeneration of mesenchymal tissues, such as bone, cartilage, fat, tendon, muscle and marrow stroma. The isolation, proliferation and characterization of human mesenchymal stem cells have recently been reported.[10]

Adult hematopoietic stem cells which renew erythrocytes, white cells and thrombocytes are well known, and can be found in other tissues.[11] Petersen *et al.*[12] showed that, under certain physiopathologic conditions, a cell population originating in or associated with rat bone marrow may act as a progenitor of two types of epithelial cells present in the liver, thus confirming previous data indicating that different classes of stem cells can exist simultaneously in the same tissue.[13,14]

Finally, Bjornson *et al*.[15] showed that neural stem cells transplanted into irradiated rats pro-

duce early hematopoietic cells.

In conclusion, the salient points emerging over recent years are that pluripotent stem cells exist in the central nervous system and neurogenesis can take place after such cells have been transplanted into adult human hippocampus. Subsequent experimental animal studies suggest that neurogenesis may also occur in other parts of the adult central nervous system.

In adult tissues, certain stem cells can be instructed to choose one pathway of differentiation by growth factors, whereas others are uncommitted (as during embryonic development) and under certain circumstances may give rise to specific cell types.[16]

Forthcoming medical challenges include the transplantation of the necessary number of stem cells from tissue cultures and the administration of key regulatory molecules or other pharmacologic agents, because *in vitro* studies have demonstrated that some factors exist that can cause uncommitted stem cells to renew themselves repeatedly when they would otherwise remain quiescent or differentiate.

Both uncommitted and regressive partially committed bone marrow stem cells seem to be interesting sources for future experimental autologous and allogeneic transplantations in the central nervous system.

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Editorial note. Previous review articles in Haematologica have examined new or alternative uses of hematopoietic stem cells.[17-21]

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