

From hematopoietic stem cells to neural stem cells

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ABSTRACT Stem cells are self-renewable, pluripotent cells that proliferate in adult life by characteristic asymmetric divisions, in which one daughter cell is committed to differentiation whereas the other remains as a stem cell. These cells are also able to differentiate into various cell types under heterotopic environmental influences. In the present study, we have explored the potential of adult hematopoietic bone marrow cells to differentiate into cells of oligodendroglial lineage under physiological, active myelinating conditions. We present evidence of oligodendrocyte generation from adult hematopoietic progenitor cells (CD117+) in vivo, after intracerebral transplantation into the neonatal mouse brain.

Differences in stem cell types depend on their location and differentiation potential (Fuchs & Segre, 2000, Weissman, 2000) and they can be transformed into heterogenic cell types by means of ectopic influences (Alison et al., 2000, Clarke et al., 2000). Mouse bone marrow cells (BMCs), or selected mouse and human MSCs have been shown to be capable of incorporating into the CNS, and differentiating into neurons, astrocytes and microglia (Eglitis & Mezey, 1997). In addition, human MSCs have been reported to develop a neuronal phenotype in vitro (Woodbury et al., 2000). Moreover, neural stem cells can generate HSCs in vivo and restore blood progenitors (Bjornson et al., 1999).

We have studied here the potential of HSCs to differentiate into oligodendrocyte progenitors under physiological, active myelinating conditions, such as those which are present in the neonatal brain. We selected BMC subpopulations enriched with, or deprived of CD117+ cells. These cells were identified by the expression of c-kit (CD117), a marker of HSCs.

Materials and Methods

Two different bone marrow subpopulations (R1 and R2) from plp-sh ble-LacZ transgenic mice were gated in the sorting protocol and grafted into the brain of neonatal (P0) mice (Fig. 1A). The R2 subpopulation was selected as an experimental cell population, containing an enriched population of c-kit (CD117+) cells in which both primitive hematopoietic progenitors (CD117+, Sca-1+) and more committed hematopoietic progenitors (CD117+, Sca-1-) are represented. The R1 subpopulation was considered as a control population. Bone marrow cells from adult plp-sh ble-LacZ transgenic mice were injected into the telencephalon of P0 C3H/He mice (Fig. 1B). Schematic representation of the localization of cell grafts in the analyzed brain sections. Donor hematopoietic progenitors were induced to differentiate into oligodendrocyte progenitors, ependymocytes, neurons and astrocytes.

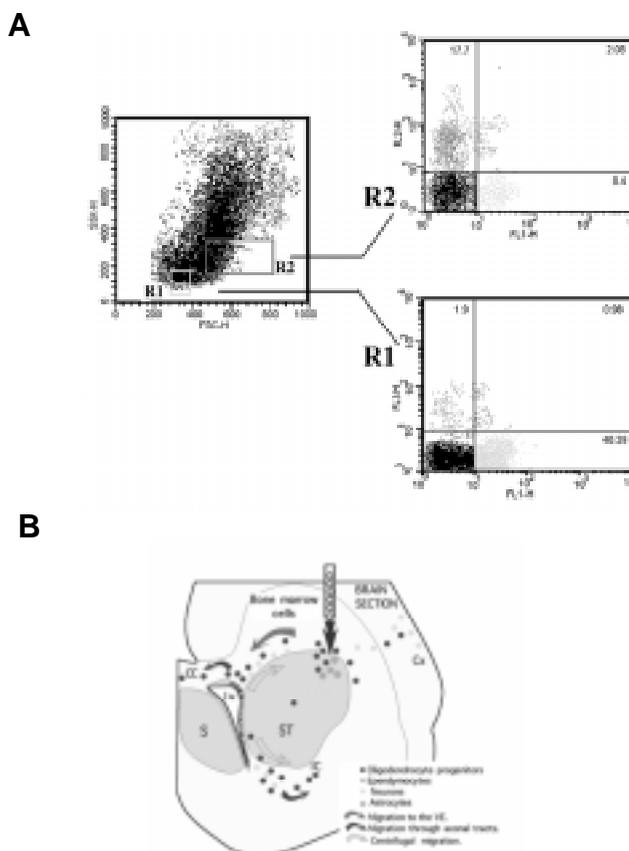


Fig. 1. Experimental procedures employed in this study. See Materials and Methods for details.

Results

Hematopoietic stem cells can be induced to develop as ependymocytes and to express oligodendrocyte, neuronal and astroglial markers. Confocal microscopic analysis of donor cells (H-2Dd+). (A,B) Ependymal cells: Section of a grafted brain showing the epithelial integration of grafted cells. The arrow shows a double stained donor oligodendrocytic cell. (C,D) Oligodendrocyte progenitors: A 1 μ m section analyzed by confocal microscopy, showing a donor cell (arrow) with double labeling in D (arrow); the arrowhead indicates a host O4+ cell. (E,F) Neurons: In the host striatum several donor cells (arrows in J and L) showed in K and

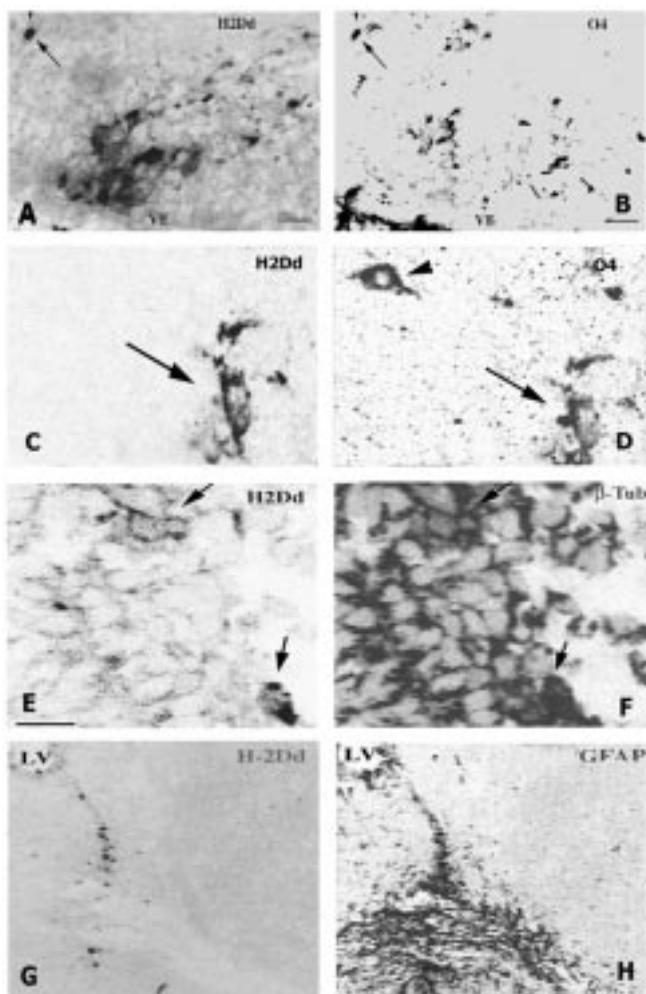


Fig. 2. Hematopoietic stem cells can be induced to develop as ependymocytes and to express oligodendrocyte, neuronal and astroglial markers. See "Results" for details.

M double staining with the neuronal marker β -III-Tubulin. (G,H) Astroglial cells: These pictures showing the intense astroglial reaction in the host injection area.

Conclusion

Our data strongly indicate that a subpopulation of adult mouse HSCs retains the capacity to differentiate into cell types other than blood cells, and more specifically into oligodendrocyte progenitors, ependymal cells, neurons and astrocytes. Thus, in adults, intrinsic genetic mechanisms of cell lineage restriction and cell fate commitment seem to retain some plasticity, *in vivo*.

Abbreviations: BMC: Bone Marrow Cell. CC: corpus callosum. CHI: Hippocampal commissure. Cx: Cortex. DT: dorsal thalamus. ET: Epithalamus. HSC: bone marrow Hematopoietic Stem Cell. IC: internal capsule. lv: lateral ventricle. ml: midline. MSC: bone Marrow stromal Stem Cell. Pi: Pial surface. S: septum. ST: striatum. VE: ventricular epithelium.

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