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BRAIN RESEARCH

Research Report

Mesenchymal and neural stem cells labeled with HEDP-coated SPIO nanoparticles: In vitro characterization and migration potential in rat brain☆

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ABSTRACT

Mesenchymal stem cells°MSC) may transdifferentiate into neural cells in vitro under the influence of matrix molecules and growth factors present in neurogenic niches. However, further experiments on the behavior of such stem cells remain to be done in vivo. In this study, rat MSC (rMSC) have been grafted in a neurogenic environment of the rat brain, the subventricular zone (SVZ), in order to detect and follow their migration using superparamagnetic iron oxide (SPIO) nanoparticles. We sought to characterize the potential effect of iron loading on the behavior of rMSC as well as to address the potential of rMSC to migrate when exposed to the adequate brain microenvironment. 1-hydroxyethylidene-1.1-bisphosphonic acid (HEDP)-coated SPIO nanoparticles efficiently labeled rMSC without significant adverse effects on cell viability and on the in vitro differentiation potential. In opposition to iron-labeled rat neural stem cells (rNSC), used as a positive control, iron-labeled rMSC did not respond to the SVZ microenvironment in vivo and did not migrate, unless a mechanical lesion of the olfactory bulb was performed. This confirmed the known potential of iron-labeled rMSC to migrate toward lesions and, as far as we know, this is the first study describing such a long distance migration from the SVZ toward the olfactory bulb through the rostral migratory stream (RMS).

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Abbreviations: BrdU, bromodeoxyuridine; BSA, bovine serum albumin; DMEM, Dulbecco's modified Eagle's medium; DPBS, Dulbecco's phosphate buffered saline; EDX, energy dispersive X-ray; FBS, foetal bovine serum; HEDP, 1-hydroxyethylidene-1.1-bisphosphonic acid; HG, high glucose; IHC, immunohistochemistry; LG, low glucose; MIAMI, marrow isolated adult multilineage inducible; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; OB, olfactory bulb; PB, Prussian blue; PFA, paraformaldehyde; RMS, rostral migratory stream; rMSC, rat mesenchymal stem cell; rNSC, rat neural stem cell; RT, room temperature; SEM, scanning electron microscopy; SPIO, superparamagnetic iron oxide; SVZ, subventricular zone; TEM, transmission electron microscopy

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1. Introduction

Stem cells are often described as the best candidates for cell therapy studies due to their self-renewal capacity and their large differentiation potential. Among them, mesenchymal stem cells (MSC) remain easy to isolate and expand. They may exhibit immunodepressive characteristics which make them less sensitive to rejection by the host immune system (Le Blanc et al., 2003; Maitra et al., 2004; Nasef et al., 2007). Moreover, MSC allow autologous grafts to be performed in cell therapy protocols. Bone marrow MSC typically differentiate into connective tissue cell types (D'Ippolito et al., 2004; Jiang et al., 2002), but various laboratories have also reported the transdifferentiation potential of MSC into a neuronal-like phenotype (Black and Woodbury, 2001; Sanchez-Ramos et al., 2000; Trzaska et al., 2007). We previously showed that a subpopulation of human MSC, marrow-isolated adult multilineage inducible (MIAMI) cells may trandifferentiate in vitro in a neurotrophin-dependent manner into neuronal-like cells. These cells express neuronal markers and present electrophysiological characteristics similar to those observed in mature neurons (Tatard et al., 2007). Moreover, a fraction of MSC transplanted in adult rat brains may respond to microenvironmental cues and transdifferentiate into neuronal-like cells (Jendelova et al., 2004; Kopen et al., 1999; Zhao et al., 2002). Using different brain lesion models, it has been shown that implanted MSC may be involved in functional improvement, either directly or indirectly by their ability to produce various growth factors (Chen et al., 2002; Li et al., 2002; Mahmood et al., 2002; Zhang et al., 2005). In addition, a damaged environment resulting e.g. from ischemia or from the presence of a tumor is known to stimulate the migration of transplanted MSC (Jendelova et al., 2004; Mahmood et al., 2002; Sykova and Jendelova, 2007a) as well as of neuronal precursors (Aboody et al., 2000; Kokaia and Lindvall, 2003). MSC may thus be considered as potential candidates for cell therapy studies in the central nervous system.

However, the possible use of MSC for brain repair studies still requires an evaluation of their behavior, migratory dynamic and fate in vivo. Moreover, as only a fraction of the transplanted cells may respond to the stimuli of the

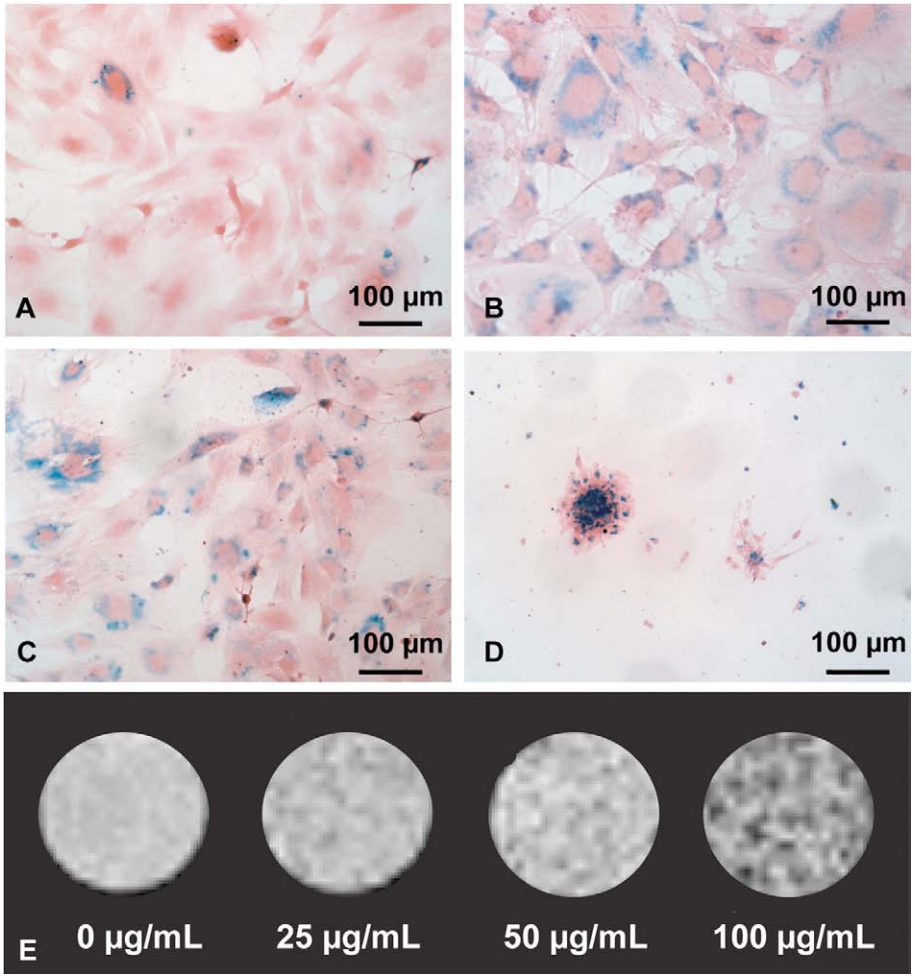

Fig. 1 – In vitro Prussian blue assessment of iron uptake and MRI. The intensity and the percentage of PB positive cells (in blue) increased with the iron concentration used. rMSC incubated for 48 h with 25, 50 and 100 µg/mL iron (A, B and C respectively). rNSC incubated for 24 h with 50 µg/mL iron under adherent conditions (D). In vitro T2*-weighted images (TE=15 ms) of an agarose gel containing rMSC incubated for 48 h in culture medium containing HEDP-coated nanoparticles (E). From left to right, iron concentration in the media was 0, 25, 50 and 100 µg/ml.