Magnetic labeling of human bone marrow stromal cells and their imaging after transplantation: an in vivo animal study

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Introduction

Bone marrow stromal cells (MSC) are pluripotent progenitor cells that have the capacity to migrate and that exhibit site-dependent differentiation in response to environmental signals. Animal experiments (1) showed that transplanted magnetically labeled rat MSC can be observed *in vivo* using MR imaging. MRI allows the tracking of their migration in an experimental animal model of brain injury, a cortical photochemical lesion. In this study we examined the fate of intravenously injected human MSC in this animal model.

Materials and Methods

A photochemical lesion was evoked in the right hemisphere of Wistar rats by rose bengal/light beam interaction 1 week prior to transplantation. MSC were isolated by their adherence to plastic from bone marrow obtained by puncture of the iliac crest of human donors under local anesthesia. The cells were labeled with the commercially available superparamagnetic contrast agent Endorem®. The Endorem suspension (100microliters per 10 ml of medium i.e., 1.1 mg of iron) was added 5 days prior to transplantation. After 72 hours the contrast agent was washed out. The cells were administered intravenously in 0.5ml of PBS into the femoral vein: Group 1 (6 animals) received 0.4 million cells, Group 2 (3 animals) received 0.7 million cells, Group 3 (6 animals) received 1.7 million cells, and Group 4 (3 animals) received 10 million cells. A control group consisted of 3 animals with a photochemical lesion only. Animals were immunosuppressed by cyclosporine A (Novartis, administered daily) and Depo-Medrol®, (UpJohn, administered weekly).
MR examination was performed 2 weeks after transplantation. MR images were obtained using a 4.7 T Bruker spectrometer equipped with a homemade surface coil. A standard T2W turbospin echo sequence was used to obtain a set of transversal images covering the whole brain, FOV=3.5 cm, matrix 256x256, slice thickness 0.5 mm. Rats were sacrificed 4 weeks following transplantation, and the brains were histologically analyzed. For iron/cell detection, Prussian Blue staining and a mouse anti-human nuclei monoclonal antibody (HuNu, Chemicon), detected using Alexa Fluor 594 goat anti-mouse IgG (Molecular Probes), were used.

Results

Two weeks after transplantation, a hypointense signal, which suggests the migration of cells to the lesion, was detected in the lesion (Fig.1). The hypointensity was detected in all animals receiving 1.7 million cells or more. Experiments with fewer transplanted cells were less successful. We detected the hypointense signal only in 2 animals (out of 6) in Group 1 and in 2 animals (out of 3) in Group 2. Histology confirmed the presence of iron in the lesion (Prussian Blue staining, see Fig. 2A). The cells in the lesion were also HuNu positive (Fig. 2B).

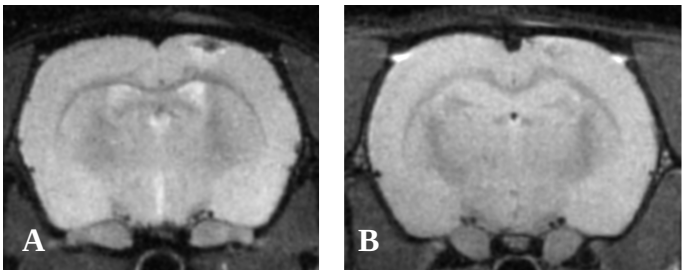

Fig. 1: An MR image of a rat brain 2 weeks after the intravenous injection of cells. A – a rat with 1.7 million cells, B – a control animal with a lesion only.

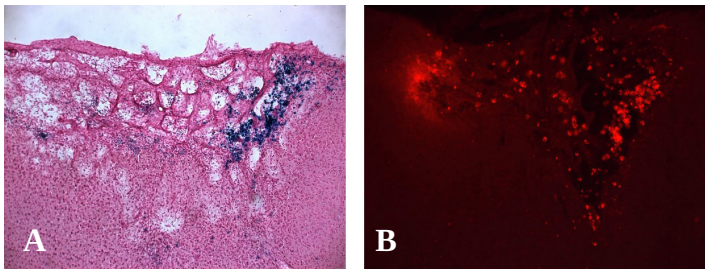

Fig. 2: Migration of MSC into a photochemical lesion 4 weeks after i.v. injection. A - Prussian Blue staining, B – Anti-HuNu staining

Discussion/Conclusion

Our study shows that a commercially available contrast agent can be used as a cell marker of human MSC for noninvasive *in vivo* MR tracking. We demonstrate that human MSC labeled with iron-oxide nanoparticles migrate into an injured site; therefore, this procedure can be used to track implanted cells in experimental animals and presumably also in patients. The study shows that given a sufficient number of cells, intravenous injection might be a viable procedure for clinical use.

References

(1) Jendelová P, Herynek V, DeCroos J, Glogarová K, Andersson B, Hájek M, Syková E. Imaging the fate of implanted bone marrow stromal cells labeled with superparamagnetic nanoparticles. MRM 2003, 50(4):767-76

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