MRI tracking Adult Neural Progenitor Cells in Brain Tumor

Q. Jiang[1,2], Z. Zhang[1,2], F. Jiang[1], G. Ding[1], R. Zhang[1], L. Wang[1], L. Zhang[1], L. Li[1], J. Hu[3], A. S. Arbab[4], Q. Li[1], M. Chopp[1,2]

[1]Neurology, Henry Ford Health System, Detroit, MI, United States, [2]Neurology, Wayne State University, Detroit, MI, United States, [3]MR Center, Wayne State University, Detroit, MI, United States, [4]Radiology, Henry Ford Health System, Detroit, MI, United States

INTRODUCTION: Using neural stem cells as therapeutic delivery vehicles, several studies reported that neural stem cells can target tumor mass and invasive satellite tumor cells and promote tumor regression[1,2]. Non-invasive methods are needed to dynamically monitor grafted neural stem cell targeting of tumor cells. Current understanding of neural stem cells targeting brain tumor cells has been derived mainly from single time point regional measurements of labeled grafted cells using histological and immunohistological methods[1,2]. MRI offers a noninvasive method for evaluation of magnetically labeled cells in the host brain [3,4]. In the present study, using MRI, we report on the in vivo monitoring of magnetically labeled neural stem cells targeting tumor mass and infiltrated tumor cells in a rat model of gliosarcoma.

MATERIALS AND METHODS: Five microliters of the 9L rat gliosarcoma cell suspension ($1x10^4$ cells) were injected into the right hemisphere at the following coordinates calculated from the bregma, AP=1mm; ML=3mm; depth=2.5. Neural stem cells were isolated from the subventricular zone (SVZ) of the adult Fisher rats and were labeled by superparamagnetic particles using a biolistic device "gene gun" [5]. Thirteen male Fisher rats were placed in a stereotaxic frame. Six microliters of PBS, containing approximately 1×10^5 superparamagnetic labeled-SVZ cells, were injected via percutaneous injection into the cisterna magna one week after gliosarcoma cell implantation. MRI measurements were performed at 1, 7, 14 and 28 days after tumor cell implantation to track migration of superparamagnetic particles labeled cells and the rats were sacrificed after the last MRI measurements. NMR measurements were performed with a 7 T, 20 cm bore, Magnex superconducting magnet equipped with a 20 G/cm, 12 cm bore gradient insert. To measure migration and localization of labeled cells, three dimensional gradient echo MR images were obtained with TR=40 ms, TE=10 ms, 32x32x16 mm^3 field of view (FOV). The 256x192x64 matrix was interpolated to 256x256x64 (0.125x0.125x0.25 mm^3) for analysis. To detect superparamagnetic labeled cells in the host brain, brain sections were stained for iron using Prussian blue reaction. Laser scanning confocal microscopy (LSCM) was used to detect green fluorescent protein (GFP) and Dil labeled cells.

RESULTS: The labeled neural progenitor cells selectively migrated towards tumor cells as detected by MRI and histology. Figure 1 shows that the transplanted labeled neural progenitor cells identified histologically colocalizes with correlates low signal intensity on MRI. Loss of MRI signal intensity was detected in the contralateral corpus callosum 5 days after transplantation of labeled neural progenitor cells in a representative rat with 9L gliosarcoma cell implantation (A, dark areas, arrow). A Prussian blue-stained coronal section of the same rat shows transplanted neural progenitor cells in the contralateral corpus callosum (B, blue cells, arrows) which correspond to low signal intensity on MRI (A, arrows). An insert in panel B is a higher magnification of blue color cells. Dark areas on MR image of coronal sections (C, arrows) correspond to DiI superparamagnetic particle-labeled neural progenitor cells in another representative rat 5 days after neural progenitor cell transplantation (D, red, arrows). By using GFP-9L gliosarcoma cells and DiI superparamagnetic particle-labeled neural progenitor cells, we also detected gliosarcoma cells were colocalized with neural progenitor cells.

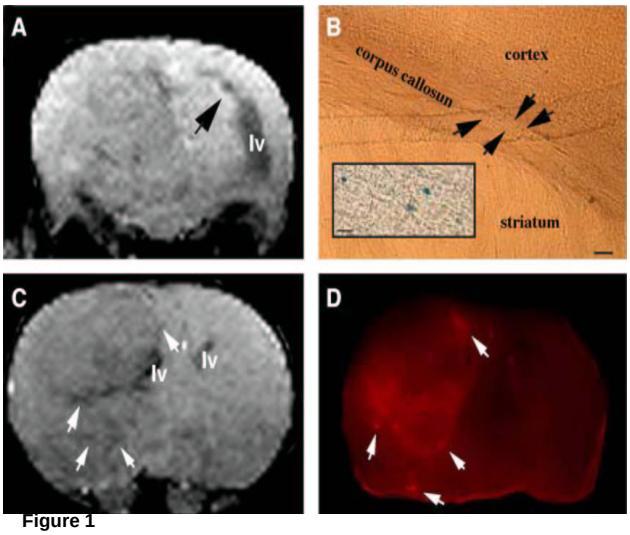

Figure 1

DISCUSSIONS: These studies demonstrate that adult neural progenitor cells target tumor cells, and MRI can dynamically monitor grafted adult neural progenitor cells migrating towards tumor mass and infiltrated tumor cells. Therefore, the MRI technique provides a sensitive method for in vivo assessment of grafted cells targeting tumor mass and infiltrated tumor cells.

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