In Vivo MRI of MR-labeled Neural Stem Cell Migration to Gliomas

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Introduction: Neural stem cells (NSC) have been recognized as cellular vehicles for treatment of invasive brain tumors (1,2). MRI is a unique non-invasive tool to monitor the migration of stem cells labeled with MR contrast agents, such as superparamagnetic iron oxide (SPIO) particles (3). Pervious studies have confirmed that magnetosonoporation (MSP) can instantly labeled SPIO into stem cells (4). The aim of this study was to validate the feasibility of MRI of MSP-labeled NSC migration to gliomas *in vivo*.

Materials and Methods: Four nude mice (6-8-week-old, Charles River Lab, Wilmington, MA) were intracranially implanted with CNS-1 mouse glioma cells and MSP/Feridex-labeled, LacZ-expressed C17.2 NSCs to the right and left hemispheres, respectively. Briefly, the mice were anesthetized with isoflurane (1-3%) and placed in a stereotactic frame. The scalp was opened to expose the skull, and a burr hole was then drilled through at the projection of 2 mm lateral and 1 mm anterior to the bregma. Under the stereotactic guidance (Stoelting, Wood Dale, IL, USA), a 27-gauge needle with a Hamilton syringe (Hamilton, Reno, NV) was inserted into brain parenchyma at 2.5-mm depth. Then, approximately $5x10^5$ glioma cells were implanted into the right hemisphere of each mouse brain at a speed of 2 μL, over 6 minutes. After this, approximately $8x10^4$ C17.2 cells were labeled with 1000ng/mL Feridex using the optimized MSP parameters of 20% duty circle, 0.3 w/cm^2 intensity, and 5-minute exposure time. Then, the MSP/Feridex-cells, suspended in 2-uL PBS, were locally injected into the left hemisphere of each mouse brain. The burr hole was then filled with bone wax and the scalp was closed with sutures. A serial in vivo MR imaging was performed at 3, 6, and 9 days after cell transplantation using a clinical Philips 3.0 T MRI scanner equipped with a surface coil. For in vivo MRI of mouse brains, we achieved T2-weighted MRI using turbo spin echo sequence (TE/TR=4000/100ms, NEX=6, and scan time=18 minutes). Following in vivo MR imaging, the animals were trans-cardiacally perfused with PBS containing 4% paraformaldehyde. Then, the brains were harvested, cryosectioned at 8-μm thickness, and stained with (i) H&E for visualization of brain/glioma anatomy; (ii) Prussian blue for detection of Feridex-positive cells; and (iii) X-gel for localization of LacZ-positive cells.

Results: In vivo following-up MRI after the cell implantations showed the area of the MR signal void at Feridex/cell-injected sites decreased, whereas the hypointense areas within or surrounding the glioma masses were visualized **(Fig. 1)**. Histopathological examination confirmed the formation of the glioma. Both Prussian blue and X-gal staining detected Feridex- and LacZ-positive cells along the migratory tracts, as well as within and surrounding the glioma masses (**Fig. 2**).

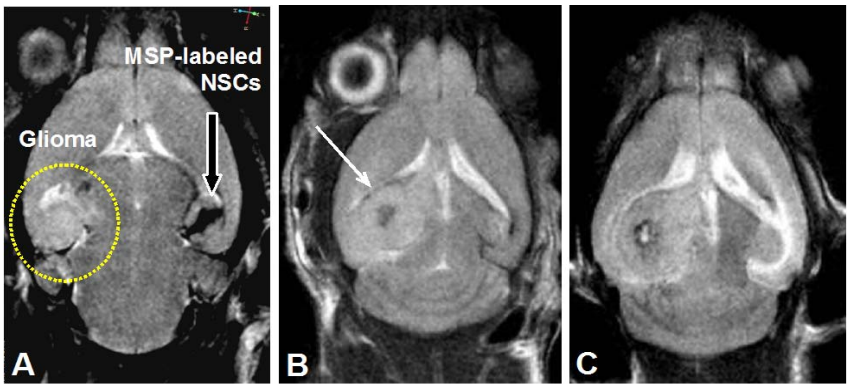

Figure 1. In vivo MRI of the migration of MSP-labeled neural stem cells to gliomas in mice. (A) T2-weighted MRI demonstrated a glioma mass in the right hemisphere (circle) and MR signal voids at the site injected with MSP-treated, Feridex-labeled cells in the left hemisphere of the mouse brain. (B&C) At days 6 and 9 post-cell implantation, the area of signal void at cell-injected sites decreased, whereas hypointense areas within or surrounding the glioma masses (long arrow on B) were detected.

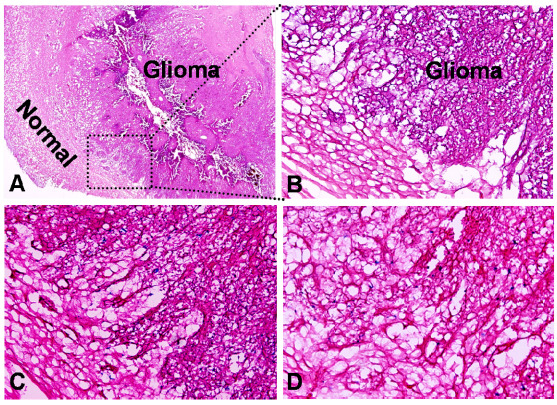

Figure 2. (A&B) Histopathological examination confirms the formation of the glioma (H&E stain). Both Prussian blue staining (C) and X-gel staining (D) demonstrated Feridex- and LacZ-positive cells, as blue-colored dots, surrounding and within the glioma mass.

Conclusion: This study has confirmed the feasibility of using MRI to track MSP-labeled NSC migration to glioma masses, which may provide a useful imaging technique to monitor NSC-based therapy for gliomas.

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Reference:

1. Snyder EY, et al. Nature 1995;374(6520):367-370.
2. Ehtesham M, et al. Cancer Res 2002;62(20):5657-5663.
3. Frank JA, et al. Radiology 2003;228(2):480-487.
4. Qiu B, et al, ISMRM 2007, May 19-25, Berlin, Germany.