Detection of Neural Stem Cells Homing into Brain Tumors Using In Vivo MRI

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Introduction

Neural stem cells have been used as experimental therapeutic delivery systems for gene therapy of both localized brain tumors by direct injection [1] and invasive tumors by intracranially distant [2] or intravascular injections [3]. A similar characteristic was also found to exist in human adult bone marrow-derived neural stem-like cells [4]. One of the important questions to be assessed before clinical implementation of such therapeutic strategies are undertaken for the treatment of brain tumor is how to monitor the tumor targeting capability of stem cells non-invasively. This issue has been addressed in a recently published study using gradient echo MRI to track iron-labeled neural progenitor cell and marrow stromal cells migrating to brain tumor using micron size iron oxide particles that have not been approved for clinical use [5]. Although the result indicates a high potential of using MRI for monitoring iron-labeled stem cells in early stage of tumor, it is not clear whether such technology is still adequate for large tumors which are accompanied with sporadic hemorrhage leading to similar susceptibility effects as iron labeled stem cells. The present study was performed to assess the capability of serial MRI in tracking of neural stem cells using clinically approved superparamagnetic iron oxide (SPIO) particles homing into large rat brain tumors for extended period of time.

Method

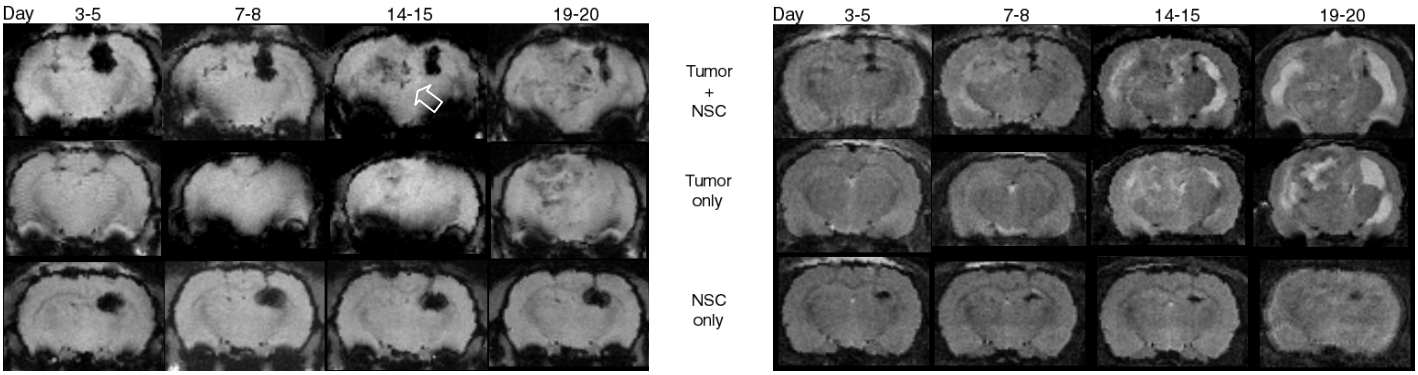
The study was conducted with F98 glioma cells and C17.2 neural stem cells. The C17.2 cells were labeled with clinically approved SPIO particles, Feridex (25 μg Fe/ml), as reported earlier [6]. Both F98 (10 μl, 2×10^4) and C17.2 (10 μl, 5×10^4) cells were implanted stereotactically (3 mm lateral and 3mm posterior to bregma; depth 3 mm from dura) into the brains of Fisher rats (n=5). For control, either F98 only (n=2) or C17.2 (n=2) cells were injected in one hemisphere along with saline in the other hemisphere.

MRI scan was performed using a 4.7 T, 40 cm horizontal bore magnet with 5 cm birdcage coil. MR images were acquired using both multislice gradient echo sequence (TR = 260 ms, TE = 20 ms, slice thickness = 1 mm, FOV = 3 x 3 cm, repetition = 16) for iron detection and spin echo sequence (TR = 2.5 s, TE = 60 ms, slice thickness = 1 mm, FOV = 3 x 3 cm) for tumor delineation. The scan was carried out at four time points; 3-5, 7-8, 14-15, and 19-21 days after cell innoculation. The animals were sacrificed at various time points for histological studies.

Results & Discussions

Fig.1 illustrates the growth of F98 tumor over a period of three weeks and the evidence of stem cell migration to the tumor regions during the same time frame (hypo-intense areas). For the animals implanted with both tumor and stem cells (top panel), most tumor growing regions have noticeably reduced MR signal intensities. This signal decrease seems to be caused by the SPIO labeled stem cells that migrated into the tumor region, particularly during the earlier time points (up to about 2 weeks as indicated by an arrow in the top panel of Fig.1a). In contrast the control animals (middle panel of Fig.1a) did not exhibit these hypo-intensities in the tumor region at these early time points. At the later time point, around 3 weeks after the implantation, when the tumor was greater than 6-7 mm in diameter, large areas of signal decrease were observed across the entire tumor with or without the stem cells, probably due to the presence of hemorrhage. The animals injected only with the SPIO labeled stem cells did not exhibit any migration of stem cells at all the time points studied (bottom panel of Figure 1a). Fig.1b shows the spin echo images of the same slices as those of Fig.1a. The tumor appears with variable signal intensities surrounded by enlarged ventricles at the later stages. The presence of the SPIO particles is also detected in the spin echo images with much lower sensitivity compared with the gradient echo images.

These results indicate the potential of using MRI and a clinically approved SPIO to non-invasively track the stem cell migration into the brain tumor region. This method appears to be most effective during the early stages before a significant amount of hemorrhage occurs. It is not yet clear whether the hypointense voxels at the later stages can be adequately attributed to either the iron labeling or hemorrhage. This will be further investigated with a larger sample size and histological studies.



(a) Gradient echo images (b) Spin echo images

Figure.1 Examples of gradient echo (a) and spin echo images (b) at various time points with three experimental paradigms.

References

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