Neuralized iPSCs can migrate to gliomas: MRI findings

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Introduction: The recent discovery of induced pluripotent stem (iPS) cells shows tremendous promise in developing patient specific stem cell therapy (1). Noninvasive MRI can be used to monitor migration of magnetically labeled stem cells to damaged or diseased tissue *in vivo* (2,3). Here, we use this MRI technique to provide the first evidence of neuralized iPS cell migration to brain tumors *in vivo* using a mouse model.

Materials and Methods: Human neuralized iPS cells (niPSC) and T98G glioma cells were cultured as monolayers in 6-well dishes. Human niPSCs were magnetically labeled with superparamagnetic iron oxide (SPIO) particles, Feridex, for MRI visualization by incubating with poly-L lysine for 48 hours at 37 °C. Feridex uptake of the cells was confirmed using Prussian blue (PB) staining and immunostaining for anti-dextran. Monolayers of T98G cells and Feridex-labeled niPSCs were harvested and resuspended in a 1:1 mixture of medium and Matrigel on ice prior to surgery. 5 nude mice were anesthetized and under stereotactic guidance T98G cells were injected into left hemisphere of the brain cortex and Feridex-labeled niPS cells were injected into the contralateral site. T1- and T2- weighted 3T MR imaging was performed 34 days after cell implantations. Mice were then euthanized and their brains were harvested and sliced for histological analysis. The sections were stained with antibodies against human DNA and dextran as well as PB staining.

Results: Human niPSC monolayers following the 48 hour incubation with Feridex, demonstrated successful labeling confirmed by PB staining. T98G and Feridex-labeled niPSCs were implanted on day 0, and the T1- and T2- weighted MR imaging was performed on day 34, as shown in Figure 1A&B. MR signal from the Feridex was nearly nonexistent at the niPSC injection site (the left side), and the contrast appeared almost exclusively at the tumor site in the right hemisphere. After harvesting and processing, the brain tissue sections were stained with antibodies to human DNA and dextran, shown in Figure 1C&D. Both implanted cells types were of human origin and thus fluoresced the red antibody used to detect human DNA. However, only dextran-coated Feridex particles fluoresced the green antibody to detect the Feridex-labeled, migrated niPSCs. The combined color image (Fig. 1D) at the tumor site showed an accumulation of iPSCs as evident by an increased signal in fluorescence, while no other areas exhibit such a high level of signal. PB staining supplemented this result, showing an accumulation of Feridex at the tumor site (Fig. 1E&F).

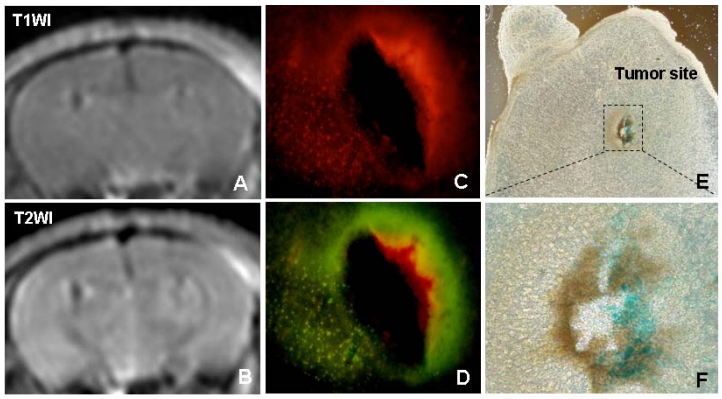

Figure 1. (A&B) MRI of Feridex-labeled niPSCs migration to gliomas showing the migrated feridex-niPSCs from the injection site in the left hemisphere to the tumor site in the right hemisphere. (C-F) Histological imaging of the tumor site stained with human nuclear antigen (red), human nuclear antigen (red) and anti-dextran (green) (C&D) and PB (E&F) showing an accumulation of niPSCs at the tumor site.

Conclusions: This study shows that niPSCs are capable of migration to brain tumors with *in vivo* monitoring using noninvasive MR labeling and imaging,an important step in the development of personalized cell therapies using an unlimited supply of patient specific stem cells.

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