In Vivo Morphological and Parametric Analysis of Stem Cell Migration on MRI: Investigation of Viable and Non-viable Behavior

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PURPOSE:

MRI can track the movement of magnetically labeled stem cells in the living brain[1,2]. However, one critical question remaining is if MRI can distinguish quantitatively viable, migrating cells from non-viable cells and the fate of the contrast agent released from dead cells. In this study, we developed a morphological and parametric analysis of *in vivo* signal intensity changes and used it to distinguish between live neural stem cell (NSC) migration and clearance of the contrast agent from the interstitial fluid.

MATERIALS AND METHODS:

Embryonic day 16 NSCs were isolated from the striatum of the fetal rat and labeled with superparamagnetic iron oxide (SPIO; Feridex IV) particles using the hemagglutinating virus of Japan envelope[3]. Approximately 10^4 labeled NSCs in 1 µL were injected intracranially into the corpus callosum (CC) of the normal Sprague Dawley rat brain (n=6). Control subjects received an injection of either diluted SPIO particles or labeled NSCs killed by a series of freeze-thaw cycles. Animals were scanned using MRI the day of transplantation and one week post transplantation with a T2*-weighted 3-D gradient echo sequence (TE=23.0 ms, TR=50 ms, FA=10°). Images were analyzed using NEUROSTAT (University of Washington). The hypointense transplantation site on co-registered images was segmented based on gray level and regional information excluding the needle track. Pixels present at one week but not at the day of transplantation were counted to represent migration. Signal intensity profiles of cells migrating along the CC at one week were parametrically modeled based on hypothesized stationary and non-stationary components incorporating Gaussian dispersion, and migration rates were estimated for the non-stationary component. Prussian blue staining was used to identify labeled NSCs on histological slices.

RESULTS:

Transplanted cells were visible on MR images and histology as they migrate (Fig. 1). The number of new pixels present at one week as compared to the initial day of transplantation based on image segmentation was significantly greater for subjects that received injections of live, labeled NSCs as compared to loose contrast agent (Feridex) or dead cells (Fig. 2, $p<0.05$). Labeled NSCs migrated laterally (n=5) and medially (n=1) along the CC, and ventrally into the striatum (n=2). Based on parametric modeling (Fig. 3), the estimated average speed of migration was 75.7±42.4, 37.1 and 59.6±20.0 (χ^2=4.7±5.4) µm/day laterally along the CC, medially along the CC and ventrally into the striatum, respectively. The estimated average speed of migration of loose contrast agent and dead cells was 9.9±14.0 (χ^2=2.1±0.7) and 9.3±11.1 (χ^2=1.7±1.0) µm/day, respectively, laterally along the CC and was significantly lower than the migratory speed of live cells laterally along the CC ($p<0.05$).

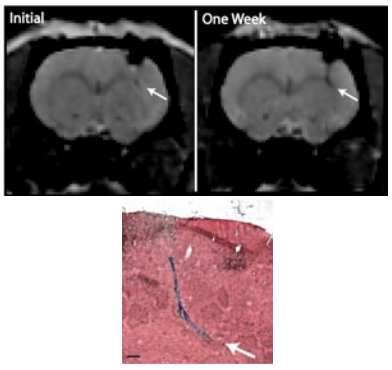

Fig. 1. 3D-GRE MRI images of NSC migration over one week (white arrows, upper) and corresponding histology (lower).

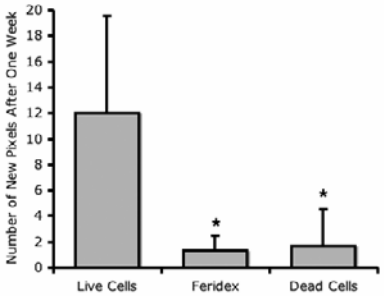

Fig. 2. Quantification of the migration of NSCs represented by new pixels segmented at one week as compared to initial on MR images.

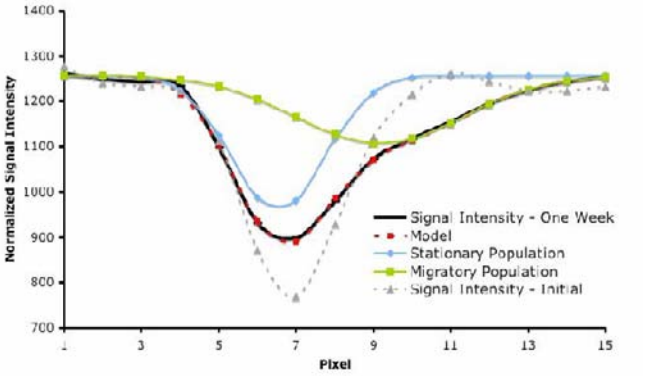

Fig. 3. Parametric modeling of NSC migration based on the separation of the line profile intensity into stationary and non-stationary (migratory) populations.

SUMMARY AND CONCLUSIONS:

These results show that cell tracking with MRI can distinguish between active cell migration and the clearance of loose contrast agent, either from dead cells or in the interstitial space. This technique represents a quantitative assay that can be used to investigate differences in migration due to factors such as cell type, brain pathology and co-administered therapeutics.

REFERENCES:

1. Bulte et al., Nat Biotechnol, 2001. 2. Hoehn et al., Proc Natl Acad Sci U S A, 2002. 3. Flexman et al., SFN Conference, Abstract 316.10, 2006.