MR Tracking Of Transplanted Cells With Positive Contrast Using Manganese Oxide Nanoparticles

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Introduction

Cell labeling with iron oxide particles is a robust method for cell tracking. Since it was initially developed [1, 2] it has been widely used for tracking transplanted cells in various organs. It has recently also entered the clinic [3]. However, in many cases it is difficult to distinguish the labeled cells from other hypo-intense regions on T2/T2*-weighted MR images. These hypo-intensities can have a physiological origin such as hemoglobin in blood, or pathological, such as blood clots or experimental procedures (e.g caused by cell injections). One attempt to differentiate iron labeled cells from blood vessels is changing the inhaled oxygen levels to reduce the BOLD effect [4]. Nevertheless, hypo-intensities on MR images remain a major obstacle for increasing the specificity of cell tracking, preventing this method from being used in certain applications, in particular those that involve trauma and hemorrhage. In order to overcome this problem we labeled cells with manganese oxide (MnO) nanoparticles as a positive T1 contrast agent that produces hyper-intensities (instead of hypo) on the MR images, and compared this to cells labeled with iron oxide particles (Feridex™).

Materials and Methods

Uniform-sized MnO nanoparticles dispersed in nonpolar organic solvent were synthesized by the thermal decomposition of Mn-oleate complex [5]. Next, water-dispersible and biocompatible MnO nanoparticles were prepared by the method described previously with some modifications [6]. Magnetoelectroporation (MEP) [7] was used to introduced the contrast agents into the 9L rat glioma cell line. $2x10^6$ cells were MEP-treated with contrast agents: Feridex 1344 ug (FeO), MnO nano-particles 68.55 ug (MnO) and (Ctrl) cells with no labeling. One day after the MEP, $2x10^5$ cells were grafted into each hemisphere of adult Fisher rats (5 rats with MnO/FeO, and 3 rats with Ctrl/FeO). The rats were scanned 24 hours after injection using a Bruker 9.4 T with MSME, (Multi Spin Multi Echo). For R1=1/T1 maps: TE=14.1 and TRs=0.2, 0.3, 0.5, 0.8 1, 1.5 2, 3, 4, 6 sec. For R2=1/T2 maps, TR=2 sec, TEs=14, 20, 30, 40, 50, 60 ms.

Results and Discussion

Figure 1 shows that FeO- and MnO-labeled cells can be detected with opposite contrast (left columns) and distinguished from unlabeled cells (right column). The MnO labeled cells can be distinguished most clearly on the R1 maps (left panel; R1=1/T1).

The main advantage of "positive labeling" is distinguishing cells from blood/hemosiderin-associated hypo-intense regions. Although some pathologies, such as tumor edema and stroke can appear as hyper-intense regions on T1-weighted images, they can be easily distinguished from labeled cells on R1 maps: the former results from an increase in tissue water content and is characterized by shortening of R1, while MnO-labeled cells result in an increase of R1. A histogram of the pixel distribution (Figure 2) reveals that the pixels from the MnO-labeled tumor cells have a higher R1, whereas the pixels from the brain tissue surrounding the tumor have R1 values similar to brain and unlabeled tumors. The contrast from MnO-labeled cells was found to decay faster than that for Feridex-labeled cells at days 2-3 after transplantation. However, both the concentration of metal used and the particle size of MnO are much lower than Feridex (MnO 20 nm, FeO 120 nm). Following these initial experiments we believe that the efficiency of MnO-labeling can be improved.

Furthermore, the use of MnO nanoparticles that create positive contrast in conjunction with FeO particles that create negative contrast could be used for double labeling, allowing for example differential detection of two different cell populations on the same imaging slice (Figure 1, merged image in lower panel).

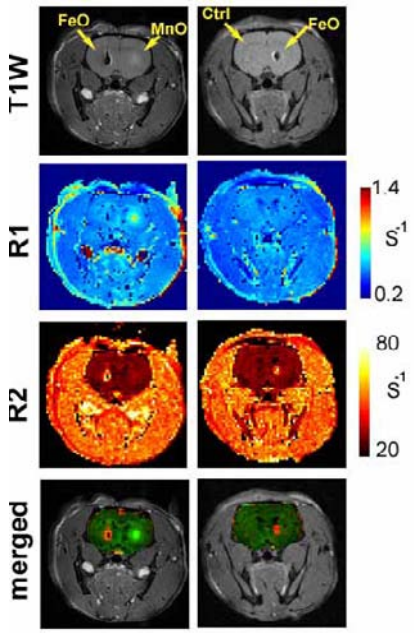

Figure 1. *T1,-weighted images R1 maps, R2 maps, and merged maps of FeO-, MnO-, and unlabeled 9L glioma cells 24 hrs after intracerebral grafting.*

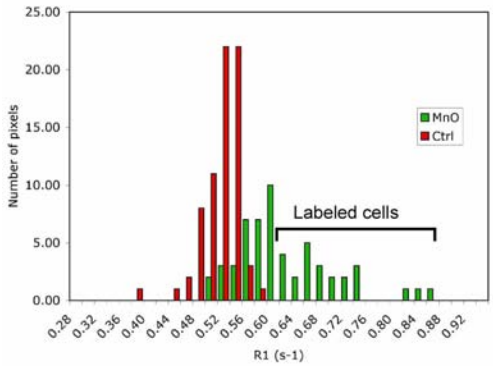

Figure 2. *R1 of each pixel is plotted for two representative rats. An ROI was selected to cover both the tumor and brain tissue. Pixels of unlabeled tumors (red, n=71 pixels) showed more uniform and lower R1 values, while MnO-labeled tumors (green, n=58 pixels) exhibit a wider spread and a shift towards higher R1 values. The overlapping pixels are from the brain tissue surrounding the labeled tumor and the "tail" can be attributed to pixels with a higher R1 due to MnO-labeled cells. The average R1 for unlabeled and MnO-labeled were 0.52s^{-1} and 0.63s^{-1}, respectively.*

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