Noninvasive MR Quantification of Magnetically Labeled Tumor Cells in Rats

W. Liu[1], D. Herzka[1], H. Dahnke[2], B. K. Lewis[3], E. K. Jordan[3], N. Banu[3], T. Schaeffter[2], J. A. Frank[3]

[1]Philips Research North America, Briarcliff Manor, NY, United States, [2]Philips Research Germany, Hamburg, Germany, [3]Experimental Neuroimaging Section, Laboratory of Diagnostic Radiology Research, National Insititue of Health, Bethesda, MD, United States

Introduction

Superparamagnetic iron oxide (SPIO) agents are used to label cells to monitor their migration and homing by MR imaging. Quantifying the number of labeled stem cells in target tissues in experimental models is of great importance to optimize dose and timing of cellular therapy in clinical trials. R2* (1/T2*) relaxation rate is a sensitive parameter for quantitative detection of intracellular SPIO [1]. This work aims to determine the quantitative relationship between the number of iron labeled cells and R2* relaxation rate in a tumor rat model.

Methods

C8161 melanoma cells and C6 glioma cells were labeled with Feridex-protamine sulfate (FEPro) complexes using procedures described previously [2]. Nude rats were implanted subcutaneously bilaterally with 2×10^6 FEPro labeled and unlabeled (control) melanoma cells (n=4) or 1×10^6 FEPro labeled and unlabeled C6 glioma cells (n= 4). MRI was performed approximately two weeks after the inoculation of the tumor cells on a 3T Intera whole-body scanner (Philips Medical System, Best, The Netherlands) using a dedicated 7cm rat solenoid rf-coil (Philips Research Laboratories, Hamburg, Germany). Regular R2* map was acquired with multiple gradient echo sequence [TR/TE = 1540/16 ms, 13 echoes, 256×256 matrix, 17 slices, Slice-thickness = 1.0 mm, FOV = 80 mm, NEX = 4]. To measure the R2* relaxation in tissues with highly concentrated labeled cells, five sets of spin echo images were obtained with the readout echo shifted 0 ms, 0.4 ms, 0.8 ms, 1.2 ms and 2.3 ms, respectively [TR/TE = 1000/6.4, 144 × 144 matrix, 17 slices, Slice-thickness=1.5 mm, FOV = 80 mm, NEX = 4]. R2* relaxation rates were calculated by mono-exponential fitting using an in-house IDL software tool. Both datasets (i.e. regular R2* map and R2* map of tissues with highly concentrated labeled cells) were combined. The R2* relaxation of the tumor was calculated as the average of pixel-wised R2* relaxation over the whole tumor volume. Number of labeled cells per mm^3 is determined as the number of implanted tumor cells divided by the tumor volume.

Results

FEPro labeling did not change the tumor's growth. There was no significant statistical difference in tumor size between labeled and unlabeled tumors. Labeled tumor sizes ranged from 1890 mm^3 to 4950 mm^3 at the time of imaging, resulting 325 to 1056 labeled cells per mm^3 in eight tumors.

FEPro labeling significantly lengthened the R2* relaxation rate of the tumor. Figure 1a and 1b illustrate R2* maps from a labeled and an unlabeled tumor, respectively. The effect of iron labeling on R2* relaxation can be further substantiated by the R2* histogram of tumors with 1056 labeled cells /mm^3 (Figure 2a) and 325 labeled cells/ mm^3 (Figure 2b). The labeled tumors developed a much wider R2* distribution as compared to the control tumor (Figure 2c). The average R2* of the tumor demonstrated a very good linear correlation with the number of labeled cells per mm^3 (Figure 3), with a correlation coefficient of 0.91 ($p<0.01$).

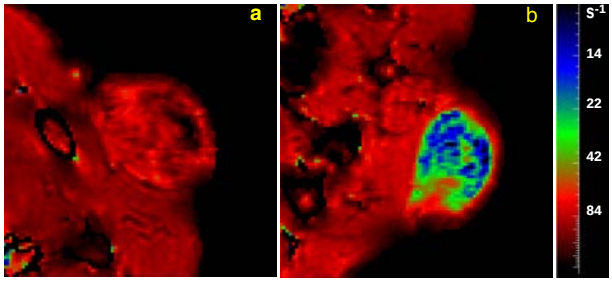

Figure 1. Representative R2* maps of (a) labeled and (b) unlabeled flank tumors.

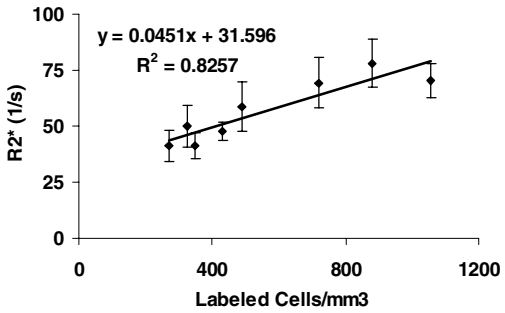

Figure 3. Tissue R2* versus number of labeled cells per mm^3. The dots are the average R2* of the whole tumor volume. Error bars represent the variations within the tumor.

Discussion and Conclusion

In this study, we investigated the quantitative relationship between the iron labeled cells and tissue R2* relaxation rate. Although two different tumor cell lines were used, the in vivo data demonstrated an excellent linear correlation between the number of iron labeled cells and tissue R2*. Our data further illustrates that R2* measurement is a reliable and sensitive tool for quantification of iron labeled cells. These results will allow quantitative assessment of iron labeled cells in vivo noninvasively.

Reference:

1. Yabloskiy DA et al. MRM 1994;32:749-763.
2. Arbab A. et al. Blood 2004;104(4):1217-1223.

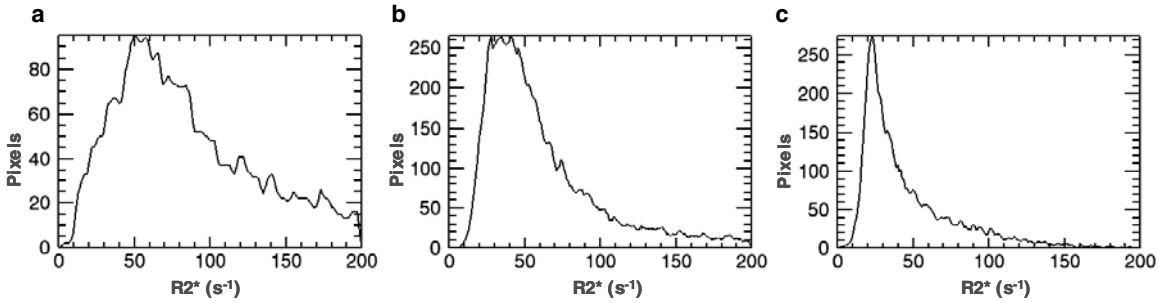

Figure 2. R2* histogram of tumors with different number of iron labeled cells: a. 1056 cells/mm^3, b. 325 cells/mm^3 and c. control.