POSITIVE CONTRAST FOR IMAGING OF RECEPTOR TARGETED MAGNETIC NANOPARTICLES IN THE ORTHOTOPIC PANCREATIC CANCER XENOGRAFT MODEL USING ULTRASHORT ECHO TIME MRI

L. Wang[1,2], X. Zhong[3], W. Qian[4], H. Chen[1,2], L. Yang[4], and H. Mao[1,2]

[1]**Radiology, Emory University School of Medicine, Atlanta, GA, United States,** [2]**Center for Systems Imaging, Emory University, Atlanta, GA, United States,**
[3]**MR R&D Collaborations, Siemens Healthcare, Atlanta, GA, United States,** [4]**Surgery, Emory University School of Medicine, Atlanta, GA, United States**

Introduction

Varieties of magnetic nanoparticles have been introduced as contrast agents for magnetic resonance imaging (MRI) and molecular imaging probes because of their superb ability in shortening transverse relaxation times T2 and T2*, which leads to a strong decrease in signal intensity of target organs or so called "negative contrast" on T2 weighted images (1,2). However, the typical drawback of the negative contrast is its poor contrast when used to study areas that have low background signals. In this study, we sought to obtain bright or positive contrast from the receptor targeted IONP probe using ultrashort echo time (UTE) imaging in vitro and in vivo.

Materials and Methods

Nanoparticles and Animal Models: IONPs with four different core sizes were prepared as previously reported (3). The averaged IONP core sizes were obtained by measuring 50 nanoparticles randomly chosen from the corresponding transmission electron microscopy images. IONP colloidal solutions at five different concentration levels for each size were prepared from the IONP stock solutions in which iron concentrations were determined by chemical analysis using a UV-visible spectroscopic method. For tumor targeting, IONPs were conjugated with single chain antibody fragment (ScFv) that binds to epidermal growth factor receptor (EGFR). Human orthotopic pancreatic cancer xenograft model was created using the MIA PaCa2 cell lines which is implanted in the mouse pancreas. Tumors typically grow to 0.5 mm^3 in 3-4 weeks before MRI experiments.

MRI Data Collection: All MRI experiments were performed on a 3 Tesla MR scanner (Tim Trio, Siemens, Erlangen, Germany) using a standard head coil. The samples or mice were placed in the iso-center of the magnet for MRI scans. To measure the T_2 of each sample, a multi-echo spin echo (SE) sequence was used with TR of 2000 ms and 20 TEs starting at 10 ms with increments of 10 ms. In addition, a UTE gradient-recalled echo (GRE) sequence described previously (4) was used to image all the samples. This sequence consists of one 60-μs long non-selective radiofrequency (RF) pulse followed by a 40-μs transmit/receive switch time, and a 100% asymmetric data acquisition from the center to the surface of a sphere in the k-space using a three-dimensional (3D) radial sampling trajectory. The ultra-short TE used for this study was 0.07 ms. Other parameters included TR = 21.7 ms, flip angle = 15°, FOV = 22 × 22 × 22 cm^3, image matrix = 192 × 192 × 192, voxel size = 1.1 × 1.1 × 1.1 mm^3, number of readout samples in one radial projection = 384, duration of one radial projection = 883.2 μs, total radial projections = 64000 and total scan time = 1391 s. For comparison, moderately T2 weighted turbo spin echo (TSE) imaging was also performed. Imaging parameters included ETL = 3, TR = 1000 ms, TE = 19 ms, image matrix = 320 × 320, pixel size = 0.7 × 0.7 mm^2, slice thickness = 1 mm and total scan time = 111 s.

Image Process and Data Analysis: MR images were analyzed using a MATLAB program (Mathworks, Natick, MA). For the images of IONP solution samples, the signal intensities from selected regions of interest (ROI) on the samples were measured. For the mice images, T2 maps were calculated with the signal intensity values at different TEs using a log-linear least-square curve fitting

Results

Example negative contrast of T2 weighted TSE images and positive contrast of UTE images of one IONP solution sample are shown in Fig.1A. MRI investigation of IONP solution phantoms show that the sizes and concentrations of IONPs are correlated to the signal intensity in UTE imaging, suggesting potential capability of UTE imaging in quantifying IONPs (Fig.1B). When applying UTE imaging of receptor targeted IONPs in pancreatic tumor models, positive contrast was also evident in animals (N=6) bearing pancreatic cancer xenograft tumors 24 hours after intravenous administration of EGFR targeted IONP probes prepared from conjugating single chain antibody ScFvEGFR with a near infrared tag NIR-830 to the IONP (Fig.2A). Orthotopic pancreatic tumors showed signal drops in T2 weighted TSE images due to the accumulation of ScFvEGFR-IONPs. In contrast, same tumors were bright in UTE imaging (Fig.2B). The positive contrast from the UTE imaging correlated well with primary pancreatic tumor and metastatic lesions detected optical imaging. The localizations of tumor and metastatic lesions by UTE imaging were confirmed by the postmortem analysis. Prussian blue stained tumor tissue sections revealed the presence of Fe positive cells bound and internalized with EGFR targeted IONPs (Fig.2C). Example colorized T2 maps and T2 weighted TSE images of one single mouse before and after IONP injection are shown in Fig.3. Colorized T2 maps show clear differentiation in tumor before and after IONP injection (Fig.3, left column). The T2 weighted TSE images show signal drop in the tumor (Fig.3, right column).

Conclusions

Our findings confirmed that UTE imaging allows for imaging of IONPs and IONP bound tumor cells with positive contrast. UTE imaging may provide contrast enhancement and potentially quantify IONPs in molecular imaging applications.
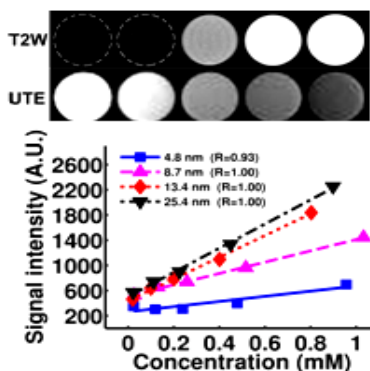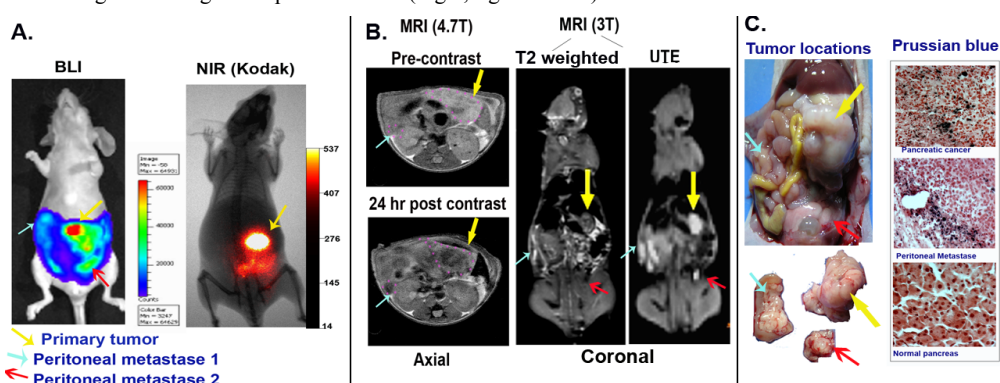

Fig 2. (A) BLI and NIR imaging showed the presence of the tumors and accumulation of ScFvEGFR-IONP-NIR850 probe; (B) Pancreatic tumors (arrows) were shown in T2 weighted TSE and UTE images with different contrast; (C) Pathology and Prussian blue staining confirmed the location of tumors and presence of EGFR targeted IONPs.
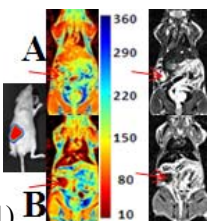
Fig 1. A: Different contrast effects of T2 weighted and UTE imaging from IONP solutions with different concentrations. B: The signal intensity of UTE images as a function of the sizes and concentrations of IONPs.

Fig 3. Tumor (arrow) showed on Colorized T2 maps (left) and T2 weighted TSE images (right) of the tumor before (A) and after (B) IONP injection.

References: [1] Simon et al. Eur Radiol 2006,16 [2] Chambon et al. Magn Reson Imaging 1993,11 [3] Duan et al. J Phys Chem C 2008,112 [4] Nielles-Vallespin et al. 17th ISMRM 2009;2654