A peptide-targeted MRI contrast agent for cancer molecular imaging

X. Wu1, M. Tan1, and Z-R. Lu1

1Biomedical Engineering, Case Western Reserve University, Cleveland, OH, United States

Introduction:

Early detection and diagnosis of malignant tumors enable more efficacious cancer treatment at an earlier stage and improvement of cancer patients' survival and quality of life. Magnetic resonance imaging (MRI) is a powerful imaging modality for cancer detection and diagnosis. However, current clinically used contrast enhanced MRI is not effective for molecular imaging because of the low sensitivity of MRI and non-specificity of the contrast agents. Safe and effective targeted MRI contrast agents are needed for cancer molecular imaging, in order to accurately detect and diagnose cancers earlier. Recently, we have identified a cancer-related biomarker, oncofetal fibronectin, as a molecular marker for cancer molecular imaging with MRI. Oncofetal fibronectin is abundantly expressed in the stroma of a broad spectrum of human malignant tumors, and rarely in normal tissues [1, 2]. Oncofetal fibronectin promotes tumor angiogenesis and proliferation. Due to its abundance in the tumor stroma, sufficient peptide targeted contrast agents can bind to the cancer-related biomarker to generate significant contrast enhancement to overcome the limitations of MRI in cancer molecular imaging. Since the peptide targeted contrast agents are smaller than the renal filtration threshold, unbound contrast agents can be readily excreted via renal filtration. In this study, we developed a low molecular weight peptide-targeted Gd(III) chelate specific to oncofetal fibronectin for cancer MR molecular imaging. The effectiveness of the agent for cancer MR molecular imaging was evaluated in an orthotopic mouse tumor model.

Materials and Methods:

Athymic nude mice bearing orthotopic human prostate cancer PC-3 were used as the animal tumor model. The animals were randomly assigned to two groups. One group was for the peptide targeted contrast agent, and the other group for a control agent with a non-targeted peptide. The contrast agents were injected at a dose of 0.03 mmol-Gd/kg into the mice via a tail-vein catheter. MR images were acquired on a 7 Tesla Bruker Biospec small animal MRI scanner with a T1-weighted gradient echo sequence before and after contrast agent injection. After MRI studies, tumor targeting of the peptide was investigated with fluorescently labeled peptides. Statistical analysis was performed using a paired two-tailed Student’s t-test.

Results:

Figure 1 shows the representative T1-weighted axial 2D gradient echo images of the tumor tissues of the mice bearing orthotopic PC-3 prostate tumor before and after injection of the contrast agents. Significant enhancement was observed in tumor tissue for targeted contrast agent. The contrast enhancement was still visible in the tumor tissues 30 min after injection. The control agent did not generate strong enhancement in the tumor tissues during the scanning period. Strong enhancement in the bladder was observed 5 min after injection of both agents, indicating that the unbound contrast agents could be readily excreted via renal filtration.

Conclusions:

We have designed and synthesized a peptide-based low molecular weight MRI contrast agent specific to oncofetal fibronectin in tumor stroma. Our preliminary results showed the targeted agent was able to deliver a sufficient amount of Gd-DOTA chelates to its molecular target. The newly developed targeted MRI contrast agent is promising for cancer MR molecular imaging.

References: