In vivo tracking of ferumoxytol labeled NK cells using MRI

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Target Audience

The target audience is scientist and clinicians who are interested in implementation of clinically approved USPIO in MRI based cell tracking and the elucidation of adoptive NK cell therapy in cancers.

Purpose

Human natural killers (NK) cells are critical components of the immune system that shows promise as a cancer immunotherapy (1,2). However, much of the underlying trafficking and targeting mechanisms of NK cells are still unknown. In this study, we investigated the trafficking of NK cells in vivo using an FDA-approved ultrasmall superparamagnetic iron oxide (USPIO) label (Ferumoxytol) and magnetic resonance imaging (MRI) in a murine tumor model. We also investigated whether the presence of the immunomodulatory agent anti-CD20-IL2 immunocytokine (ICK) will promote tumor trafficking of NK cells in a murine tumor model.

Methods

Six to eight week old athymic nude (n = 4) and NOD-scid-gamma^{null} (NSG) (n = 2) mice were implanted Daudi Burkitt's lymphoma ($3x10^6$ cells) subcutaneously in the right high groin. Tumors were 200-400 mm^3 at the time of imaging. Experimental procedures were performed in accordance with the policies of the Research Animal Care Commitees at Caltech. NK cell labeling consisted of incubation with Ferumoxytol with protamine sulfate for 2 hrs. Labeled-NK cell uptake was determined by using R2* mapping with a 6 echo multi-gradient echo (MGE) sequence in a 7Tesla Bruker scanner. Sequence parameters were as follows: TR/TE = 865ms/3.7ms (with an echo spacing of 4.8ms), matrix size = 233 x 167, resolution = 0.150 x 0.150 mm^2, slice thickness = 0.754 mm. Baseline scans were acquired, followed by labeled-NK cell injection (10×10^6 cells per dose) and then scanning continues up to 1 hr. T2o hrs prior to NK cell injection, animals were orbitally injected with saline or ICK. A 245hr scan was also obtained. ΔR2* values were computed, which was defined as the percent change in R2* value from the pre scan.

Results

Administration of labeled-NK cell resulted in significant T2* signal decrease (Fig.1), which corresponded to increased R2* values and correlated with labeled-NK cell uptake in regions of interest (tumor, liver and spleen). Across all the subjects demonstrated significant increase at the tumor site at the 1 hr time point only. Liver and spleen tissues showed significantly high ΔR2* at both times..

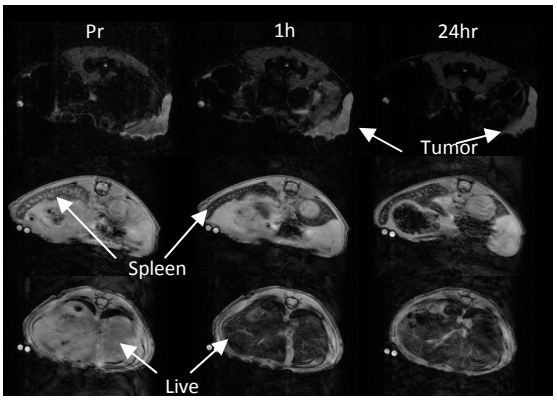
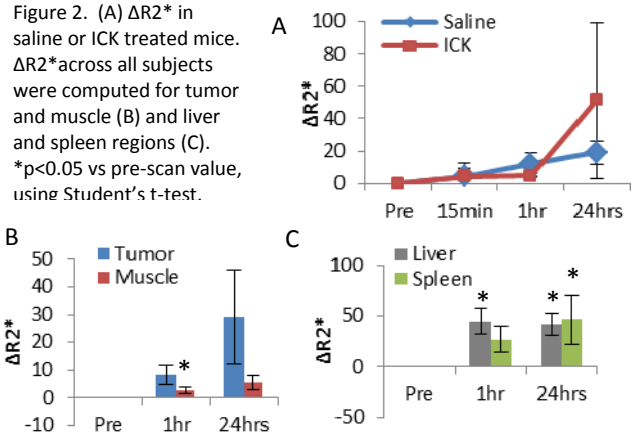


Figure 1. T2*-weighted MGE scans at pre, 1hr and 24hrs time points. Post ferumoxytol-labeled NK cells showed significant T2* signal decrease, which correlated to NK cell uptake.

Figure 2. (A) ΔR2* in saline or ICK treated mice. ΔR2*across all subjects were computed for tumor and muscle (B) and liver and spleen regions (C). *p<0.05 vs pre-scan value, using Student's t-test.



Discussion

MRI can provide a noninvasive tool to characterize adoptive NK cell therapy. We aimed to implement MRI-based NK cell tracking methods that could be clinically translatable by using an FDA-approved USPIO cell label on NK cells isolated from human peripheral blood. MRI as a noninvasive in vivo cellular imaging technique could further elucidate optimization of adoptive NK cell transfer as a cancer therapy.

References

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2. Oldham RK, Herberma.Rb. Evaluation of Cell-Mediated Cytotoxic Reactivity against Tumor Associated Antigens with I-125-Iododeoxyuridine Labeled Target-Cells. J Immunol 1973;111(6):1862-1871.