Immunocytokine facilitation of natural killer cells accumulation in tumors

Naomi S. Sta Maria[1], Samuel R. Barnes[1], David Colcher[2], Andrew A. Raubitschek[2], and Russell E. Jacobs[1]

[1]Biology and Biological Engineering, California Institute of Technology, Pasadena, CA, United States, [2]Cancer Immunotherapeutics & Tumor Immunology, City of Hope, Duarte, CA, United States

Target Audience

The target audience is scientists and clinicians who are interested in multimodal immunotherapy in cancer and in using MRI for non-invasive evaluation of adoptive cell transfer efficacy of natural killer (NK) cells.

Purpose

We investigated the accumulation of natural killer (NK) cells in colorectal adenocarcinoma tumors after priming with M5A-IL-2, which is a monoclonal antibody-cytokine fusion protein (immunocytokine, ICK), using an FDA-approved ultrasmall superparamagnetic iron oxide (USPIO) label (ferumoxytol) and magnetic resonance imaging (MRI). The monoclonal antibody portion M5A targets carcinoembryonic antigens (CEA) on the cell surface of colorectal cancer cells, whereas the cytokine portion IL-2 regulates immune responses by activating NK cells and promoting T-cells differentiation (1). M5A-IL-2 can find adenocarcinoma tumor cells and could potentiate the antibody dependent cell-mediated cytotoxicity (ADCC) of NK cells (1,2).

Methods

Experimental procedures were performed in accordance with the policies of the Research Animal Care Committees at Caltech. Six to eight week old NOD-scid-gamma^{null} (NSG) mice were implanted with human colorectal cancer cell line, LS-174T.luc (6e5 cells), subcutaneously in the right high groin flank. Tumors were 200-400 mm^3 at the time of imaging. Animals were divided into (+) ICK (n=7) and (-) ICK (n=6) groups. Human NK cells were labeled following using simple incubation with ferumoxytol (Feraheme, AMAG Pharmaceuticals, Inc.) and protamine sulfate (APP Pharmaceuticals, LLC) for 2 hours following labeling procedures from Galli et al (3). NK cells accumulation was determined using R2* mapping with a 6 echo multi-gradient echo (MGE) sequence in a 7 Tesla Bruker scanner. Tumors were scanned pre and post (5hr and 10hr) injection of labeled NK cells (10e6 cells, i.v. via tail vein). Sequence parameters were as follows: TR/TE = 600 ms/ 3.74 ms (4.78 ms echo spacing), matrix size = 233 x 167, resolution = 0.150 x 0.150 mm2, slice thickness = 0.754 mm. ΔR2* values were computed, which was defined as the difference between R2* values at the post and pre time points. All animals received 2 doses of 200µl (300 mg/ml,i.p.) intravenous immunoglobulin (IVIG), once every 3rd day, one week prior to imaging. The (+) ICK group received 200 µl (0.25mg/ml, s.c.) of ICK once daily for 4 days. The 4th dose was given 1.5hr prior NK cell injection.

Results

Representative R2* images and histogram distributions are shown in Fig1A and 1B. Distribution shifts show increased R2* values at later time points when ICK was given (Fig1B). Wilcoxon rank sum test showed a significant difference between (-) ICK and (+) ICK groups 10hr post NK cell injection (* p=0.015) (Fig1C). Tumor priming with immunocytokine pretreatment showed increased R2* values post NK cell administration, reaching significance from baseline at the 10hr time point (Pre vs. 10hr, Wilcoxon rank sum, *p=0.0012, Fig 1D).

Discussion

Using an FDA-approved USPIO label, tracking NK cell as a treatment could be readily translate into the clinic. Parametric R2* maps can provide a noninvasive in vivo assessment of labeled NK cells accumulation in various tumor models. NK cells show more effective adoptive transfer in a multi-immunotherapy setting with the administration of appropriate tumor-specific immunocytokines.

References

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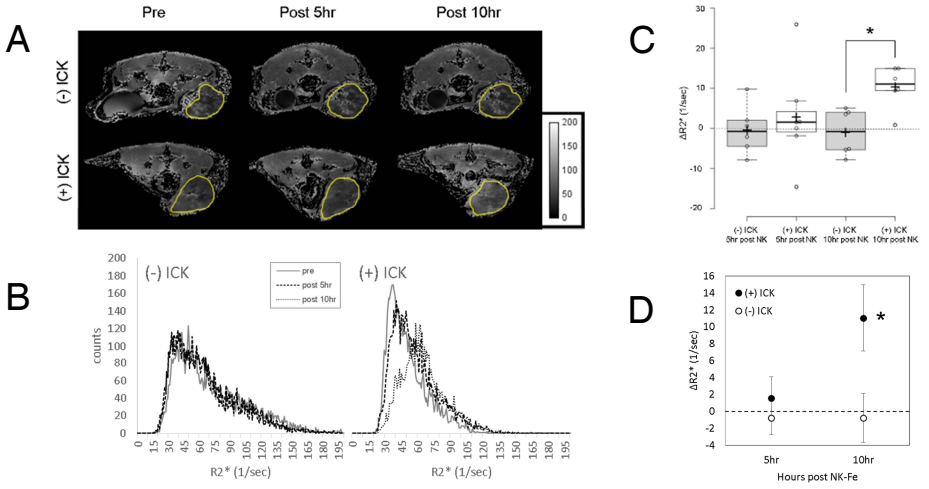

Figure 1. A. Representative axial parametric R2* images of (+) ICK and (-) ICK at pre, 5hr post and 10hr post NK cell injection. Yellow outlines show tumor regions of interest. Units in 1/sec. **B.** Corresponding R2* histogram distributions of whole tumors from (A). **C.** Box plots of ΔR2* from pre time point at 5hr and 10hr post NK injection. **D.** Median ± confidence interval (1.2*IQR/sqrt(n)) of (+) ICK and (-) ICK groups.