MRI Patterns of Signal Loss in the Liver are Related to Cell Survival or Non-Survival after Transplant of Magnetically-Labeled Immune Cells

S. A. Anderson[1], E. K. Jordan[2], Y-W. Chu[3], A. S. Arbab[2], R. E. Gress[3], J. A. Frank[2]

[1]NINDS, NIH, Bethesda, MD, United States, [2]ENS, LDRR, NIH, Bethesda, MD, United States, [3]ETIB, NCI, NIH, Bethesda, MD, United States

All intravenously administered cells reside for some period of time in the liver. Differences in their distribution in the liver dependent on cell viability or state of stimulation has not been reported. Noninvasive MRI could provide previously unavailable depiction of the distribution and the state of the cells following transplant. We have observed distinct signal intensity patterns on hepatic MRI following infusion of magnetically labeled stimulated lymphocytes or splenocytes in mice with direct-induction experimental autoimmune encephalomyelitis (EAE) distinguishable from the MRI of normal mice receiving unstimulated naïve T-cells. The purpose of this study is to compare hepatic MRI and histology demonstrating the marked differences in the cells distribution that is indicative of labeled cell survival. **Methods:** EAE model: Lymph node cultures from female SJL mice were cultured with PLP and splenocytes cultured with 0.1 μg/mL Il2 overnight prior to labeling. Naïve T-cell Model: Spleen and LN cells were harvested from donor mice (C57BL/6 mice containing the GFP transgene driven by the proximal LCK (pLCK) promoter.) T-cells were purified by negative selection using MACS T-cell isolation columns and cells were counted and labeled directly. All cells were labeled with Ferumoxides-Protamine sulfate complexes (1) and administered at a dose of 20-25M via tail vein. Mice were imaged serially on a 7T horizontal bore imaging system (Bruker, Billerica, Mass), and euthanized at each time point. MR microscopy was performed at 7T on fixed liver at 50-60 micron isotropic resolution. Microscopy was performed on Prussian Blue (PB) stained fixed sections with a Zeiss Axioplan2 imaging microscope. **Results:** In the EAE model, the liver was strongly hypointense at day 10, and had a marked mottled pattern at day 17 on both *in vivo* and *ex vivo* MRI. By 24 days the liver was uniformly hypointense similar to livers from mice receiving unlabeled cells. Microscopy showed intact iron labeled cells in liver circumventing the hepatic lobule portal triads. In comparison the mice receiving naïve T-cells had uniformly hypointense liver on MRI and on microscopy showed scattered PB positive cells-in the sinusoids of the mice receiving naïve cells. **Conclusions:** Different patterns in the liver on MRI and histopathology of the labeled cells was observed that depended on experimental conditions of the mice. The results suggest that in the naïve mouse model, labeled cells did not survive after a period of time based on the predominant appearance of PB staining Kuppfer-like cells. Additional studies are underway to delineate the contributions of cell culture and pre-existing inflammation on the fate of immune cells in the liver.

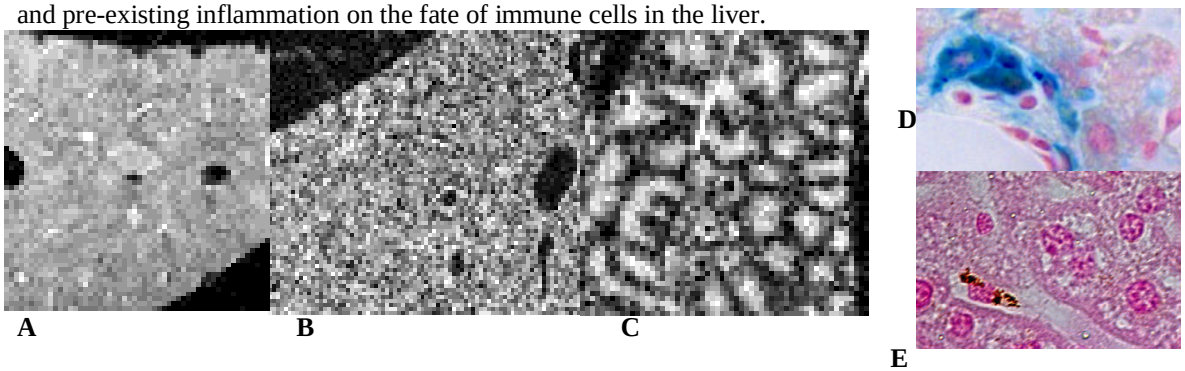

Fig. 1. A-C: 3D MRI of A, normal, B transplanted naïve splenocytes, C transplanted splenocytes with Il2 in EAE model. D. PB stain (40x) of EAE model liver with splenocyte transplant; E. DAB-enhanced PB stain (100X) of liver with naïve lymphocyte transplant.

References: 1. Arbab *et al.* Blood 2004 104(4):1217