Hyperpolarized 13C MR Spectroscopic Imaging in a Regression Study of a Switchable RAS-Oncogene Model of Liver Cancer

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Introduction:
Hyperpolarized technology using dynamic nuclear polarization has been developed and used in detecting signals of ^{13}C metabolites *in vivo* at very high SNR [1]. In this work, hyperpolarized ^{13}C 3D-MRSI using a 3D compressed sensing sequence [2] was used to measure liver metabolism in mice which developed abnormal size of the liver after expression of the RAS oncogene was switched on in the liver. After the liver developed into an abnormal state at a relatively late stage, the regression of the later disease stages before and after turning off the oncogene were studied, and significant differences in hyperpolarized lactate and alanine levels were detected.

Methods: RAS/LAP-tTA double-transgenic mice can be switched on and off with doxycycline administration [3]. The RAS oncogene was switched on and proton anatomic images were conducted every week to follow the development of the liver, which develops into an abnormal state with much larger size compared to normal liver. In the late stage of abnormal liver development, C13 studies were conducted, then the oncogene was turned off by doxycycline, and in a week a second C13 scan was conducted to follow up on how the abnormal liver regressed. All studies were performed on a GE 3T scanner with a custom $^{1}H/^{13}C$ mouse coil. ^{13}C 3D-MRSI data (TE/TR = 140ms/215ms, 0.034 cm^3 voxel size, 16 second acquisition time) were acquired with a double spin-echo compressed sensing pulse sequence [2] after injection of 0.35 mL of 80mM hyperpolarized $^{13}C_1$-pyruvate. The lactate area/(pyruvate + pyrvate hydrate) ratio was derived from the spectral arrays. The same method was used for control mice in which the oncogene was never turned off during the studies. The method was also repeated on a subset of mice with copolarization of urea and $^{13}C_1$-pyruvate.

Results: Figure 1a shows a representative case of disease status. Dramatically elevated lac/pyr was observed at the late stage of abnormal liver state, and the liver size was much larger as shown on anatomic images. Figure 1b shows the case of disease regression after RAS expression was switched off with doxycycline. Reductions in both tumor size and lac/tCar were observed. Figure 2 shows the spectrum under the same conditions as Figure 1 with copolarization of urea and $^{13}C_1$-pyruvate. Figure 3 shows lac/pyr data from all mice studied. For lac/pyr, statistically significant differences were detected between late stage disease and the regressed state.

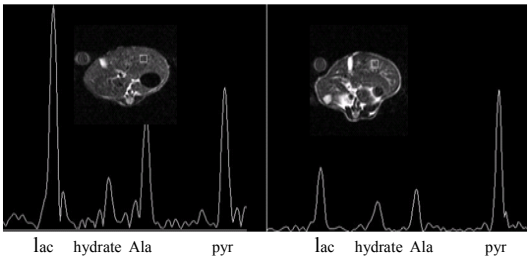

Fig.1 A Fig.1 B

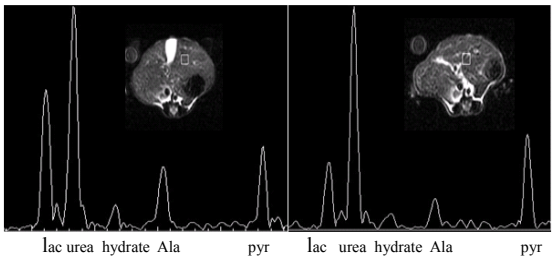

Fig.2 A Fig.2 B

Figure 1 and 2: A) Representative example of late disease stage after switching expression of RAS on. Elevated hyperpolarized lactate was detected. B) Representative example of disease regression after switching expression of RAS off for a week. A dramatic reduction in hyperpolarized lactate was detected. In Figure 2, a copolarization of pyruvate and urea (spectrum next to lac) was injected, and urea provided a perfusion reference.

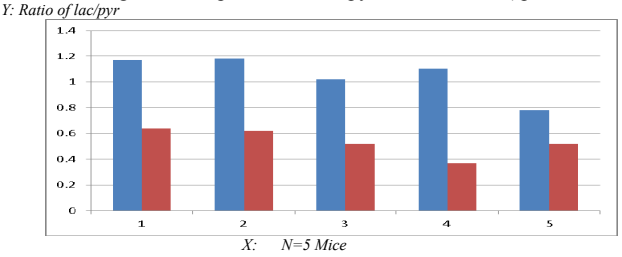

Figure 3: Multiple tests (n = 5 experiments) showed a statistically significant difference in the ratio of lac/pyr between late stage disease (blue bar) and regression state a week after the RAS oncogene was switched off (red bar).

Discussion: The inducible transgenic animal model allowed for direct analysis of *de novo* tumor formation driven by a defined oncogenic event. Metabolic changes following RAS deactivation were monitored by using hyperpolarized [1-^{13}C]pyruvate to probe the LDH pathway. Significant changes in hyperpolarized lactate levels were detected with oncogene expression and inhibition. This study demonstrated the potential of hyperpolarized ^{13}C to monitor cancer regression and gene therapy in the liver.

References: [1] Ardenkjaer-Larsen et al. PNAS (2003) 100:10158 [2] Hu et al. MRM (2010) 63:312 [3] Shachaf et al. Nature (2004) 431:1112

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