In vivo Monitoring of Enzyme Activity in a Transgenic Breast Cancer Model with Hyperpolarized C-13 Metabolic Activity Decomposition MRSI

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Purpose: The ability to measure alterations in enzymatic activities in vivo can be applied to monitor tumor progression and regression and has the potential to guide and augment invasive biopsy-based assays[1]. Recently, the concept of Metabolic Activity Decomposition Stimulated-echo Acquisition Mode (MAD-STEAM) was developed to quantify metabolic conversions based on phase-sensitive detection[2]. The goal of this project was to develop a spatially localized, dynamic MAD-STEAM spectroscopic imaging sequence to monitor localized enzymatic activity changes in a switchable oncogene-driven breast cancer mouse model.

Methods: For *in vivo* animal experiments, a 3T clinical MRI system (GE, Waukesha, WI, USA) was used with a ^{1}H-^{13}C dual tuned, birdcage coil. Under the MAD-STEAM acquisition, newly converted metabolites with Δf chemical shift would accrue phase of $\Delta\varphi = 2\pi\Delta f TE/2$. This phase information enabled the differentiation of newly generated spins from existing ones thus providing direct information on the rate of enzymatic conversion[2]. The pulse sequence uses flyback-EPSI readout for simultaneous spectral encoding with 1D spatial localization of tumor and normal tissue voxels, and was repeated for dynamic acquisitions. Two adiabatic double spin echo pulses were used before data acquisition to extend the echo time, reduce sensitivity to phase errors, and improve spectral quality[3]. ^{13}C-urea was co-polarized to serve as a reference to correct for phase shifts experienced by all spins. The tumor growth was controlled by doxycycline, which activated MYC transcription and induced tumor progression; and in the absence of the doxycycline, MYC expression was inhibited and induced tumor regression.

Theory: Metabolite T_1 values and conversion rates were estimated by fitting integrated dynamic peaks to the following set of equations[4] (Figure 1).

$$\frac{d}{dt}\begin{bmatrix} Orig\,\{M_{Pyr}(t)\} \\ New\,\{M_{Pyr}(t)\} \\ Orig\,\{M_{Lac}(t)\} \\ New\,\{M_{Lac}(t)\} \end{bmatrix} = \begin{bmatrix} -\rho_{Pyr} - K_{Pyr\to Lac} & 0 & 0 & 0 \\ 0 & -\rho_{Pyr} & K_{Lac\to Pyr} & 0 \\ 0 & 0 & -\rho_{Lac} - K_{Lac\to Pyr} & 0 \\ K_{Pyr\to Lac} & 0 & 0 & -\rho_{Lac} \end{bmatrix} \begin{bmatrix} Orig\,\{M_{Pyr}(t)\} \\ New\,\{M_{Pyr}(t)\} \\ Orig\,\{M_{Lac}(t)\} \\ New\,\{M_{Lac}(t)\} \end{bmatrix}$$

Results and Discussion: Compared to normal tissue, tumor tissue showed increased pyruvate to lactate conversion rate ($K_{Pyr\to Lac}$) in the breast tumor mouse model by using the MAD-STEAM EPSI sequence. Additionally, decreased $K_{Pyr\to Lac}$ was observed within tumor regions when tumor was in the regression stage, while the normal tissue showed similar conversion rates at different stages (Table 1). These results show that dynamic MAD-STEAM EPSI detects altered tumor enzyme activity.

Table 1: LDH activity rate $K_{Pyr\to Lac}$ (in sec^{-1}) of tumor and normal tissue at different tumor growth stage

	Tumor Progression Stage	Tumor Regression Stage
Tumor	**0.14**	**0.08**
Normal Tissue	**0.04**	**0.03**

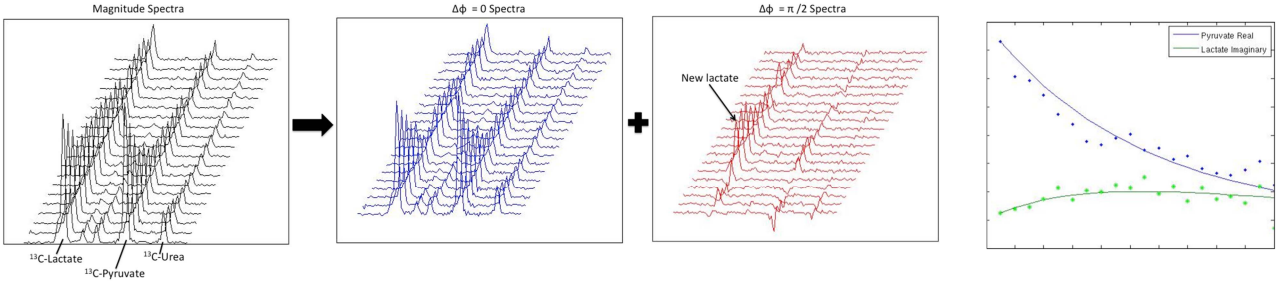

Figure 1: Magnitude spectra could be decomposed into real and imaginary components, and dynamic peak areas are fitted to the two-site exchange model to find conversion rates and relaxation times of metabolites.

Conclusions: By applying dynamic MAD-STEAM EPSI to the switchable oncogene-driven model, we demonstrated its ability to detect tumor enzymatic changes prior to any detectable anatomical changes. This could provide great benefit to the field of oncology, since it could be applied to evaluate drug and treatment effectiveness.

References: [1] Swisher et al. Magn Reson Med. In revision (2014). [2] Larson et al. J Magn Reson, 225: 71-80 (2012). [3] Cunningham et al. J Magn Reson, 187(2): 357–362 (2007). [4] Swisher et al. Magn Reson Med, 71:1-11 (2014). **Acknowledgement:** This study is supported by NIH grants P41EB013598, R00EB012064, and R01CA170447