Detecting Brain Tumor Therapy Responses Using Amide Proton Transfer Contrast

J. Zhou[1,2], P. C. van Zijl[1,2], A. Salhotra[3,4], P. Z. Sun[1,2], B. Lal[3,4], J. Laterra[3,4]

[1]Dept. of Radiology, Johns Hopkins Univ., Baltimore, MD, United States, [2]F.M. Kirby Center, Kennedy Krieger Institute, Baltimore, MD, United States, [3]Dept. of Neurology, Johns Hopkins Univ., Baltimore, MD, United States, [4]Dept. of Neurology, Kennedy Krieger Institute, Baltimore, MD, United States

INTRODUCTION: It was recently demonstrated that it is possible to produce endogenous mobile protein and peptide-based MRI contrast using a chemical exchange saturation transfer (CEST) enhancement scheme (1,2) for the amide protons in these molecules. Although the concentration of these tissue proteins and peptides is only in the millimolar range, a detection sensitivity of several percent in water signal (molar concentration) can be achieved. This approach, called amide proton transfer (APT) imaging (3), was shown to be sensitive to pH changes due to the effect of pH on proton exchange, and was able to provide brain tumor contrast due to a higher protein/peptide concentration in rat gliomas (4). We demonstrate here that APT may be used as an early marker for detecting brain tumor therapy responses.

MATERIALS AND METHODS: Fisher 344 rats (n = 7) received 9L gliosarcoma cells by stereotaxic injection to right caudate/putamen. On post-implantation day (PID) 7, three rats received 15 cGy cranial irradiation as a single fraction (Shepherd Mark I 137). On PID 10, isoflurane anesthetized rats were imaged using a horizontal bore 4.7 T Biospec animal imager with a 4 cm I.D. volume coil for RF transmission and reception. A continuous weak RF field (2 μT) of 4 sec was used for off-resonance saturation. Single-shot spin-echo EPI was used for data acquisition (TR = 10 sec, TE = 30 msec). The imaging matrix was 64×64, FOV was 28×28 mm^2, and the imaging slice thickness was 2 mm. RF saturation was done as a function of frequency offset relative to water, leading to so-called z-spectra in which the effect of the saturation transfer of exchangeable protons to water is monitored. APT images were acquired using frequency-labeling offsets of ± 3.5ppm (16 scans).

RESULTS & DISCUSSION: Figure 1a & c shows standard z-spectra (saturated imaging signal intensities normalized with respect to unsaturated) in rats without treatment (4 rats) and with treatment (3 rats), respectively. There is a small APT-based dip at the offset of 3.5ppm, which is larger in tumor (blue & open) than in contralateral tissue (green & solid). To selectively assess the APT effect without interference of conventional MT and direct water saturation, including the T_2 effects, we performed an asymmetry analysis by subtracting MT ratios (MTR) obtained at the negative offset from those at the corresponding positive offset with respect to water. The results (Fig. 1b & d) show an increase in the tumor MTR_{asym} spectrum over a range of offsets between 2-5ppm from the water, with a maximal difference at offset 3.5ppm. This range corresponds closely to the broad amide proton frequency of ~8.25ppm since 4.75ppm is the true water NMR frequency. MTR_{asym}(3.5ppm) includes two parts (3,4): the inherent asymmetry of the solid-phase MT effect associated with immobile macromolecules and membranes, and the proton transfer ratio for the amide protons (APTR) associated with mobile cellular proteins and peptides. Increased MTR_{asym}(3.5ppm) or APTR in tumor can be attributed to increased protein/peptide content or increased intracellualr pH (pH_i) in the tumor with respect to the normal region. Because only a small pH_i increase is often detected in tumor (5,6), increased protein/peptide content should be a dominating factor.

Figure 1e compares the MTR_{asym} difference (d minus b) between treatment and non-treatment. The unchanged contralateral MTR_{asym}(3.5ppm) means unchanged APTR, and a decreased tumor MTR_{asym}(3.5ppm) for treatment (~0.8%) means decreased APTR, which can be attributed to decreased cellular protein/peptide content and/or decreased pH_i in the tumor in response to radiotherapy. Comparison of quantified APTR with other measured MR parameters for treatment (3 days) and non-treatment is listed in Table 1, in which the contralateral APTR (2.94%) was that measured previously (3,4). The student's T-test shows that tumor APTR and T_1 have significantly different means between treatment and non-treatment ($P < 0.05$), but ADC_{av} and T_2 not.

Table 1	T_2 (ms)	T_1 (s)	ADC_{av} (10^{-9} m/s)	APTR (%)
Contr., Non-treatment	58.0 ± 1.8	1.46 ± 0.02	0.71 ± 0.04	2.94
Tumor, Non-treatment	80.2 ± 1.7	1.92 ± 0.07	1.19 ± 0.04	7.22 ± 0.46
Contr., Treatment	57.9 ± 0.7	1.44 ± 0.02	0.70 ± 0.04	2.94
Tumor, Treatment	79.4 ± 3.1	1.80 ± 0.04	1.22 ± 0.14	6.39 ± 0.04

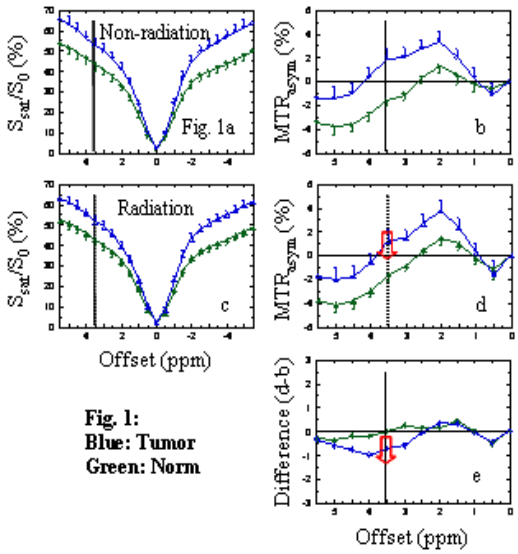

Fig. 1:
Blue: Tumor
Green: Norm

CONCLUSION: APT imaging offers a novel method to assess tumor therapeutic efficacy through monitoring cellular pH and/or mobile protein and peptide concentration changes.

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