Monitoring extracelluar pH, spatial heterogeneity and contrast agent uptake in lymphoma tumor growth with acidoCEST MRI

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Introduction: Low Extracelluar pH (pHe) is a hallmark of the tumor microenvironment.[1] A non-invasive MRI method, term "acidoCEST MRI", was used to accurately measure pHe and assess tumor acidosis.[2] The pixel-wise pHe mapping allows us to access spatial heterogeneity and also contrast agent uptake. We have applied acidoCEST MRI to monitor the effects of tumor growth in a tumor model of lymphoma, and correlate results from acidoCEST with VEGF biomarkers.

Methods: A CEST-FISP pulse sequence (2.8 μT, 5 sec, 90 Hz),[2] with 54 saturation frequencies (+10 to -10 ppm) was used to acquire an acidoCEST image in 4.8 min on 7T MRI scanner. acidoCEST were performed on Raji, Ramos and Granta519 xenografts over a period of 2-3 weeks. A bolus of 200 μL of 976 mM iopromide was injected i.v., followed by an infusion of 150 μL/hour of iopromide. Six series of acidoCEST spectroscopic images were acquired for 28 min. Groups of 3 x 3 adjacent pixels were binned, and each CEST spectrum was fitted to a single function that consisted a sum of three Lorentzian line shapes (Matlab R2012B).[3] CEST effects greater than 2√2 noise were included in the calculation of pHe[2] and % contrast agent (CA) uptake (equation B). White pixels represented pH 7 or greater (Figure C). The mice were euthanized and VEGF-A staining was carried out on these xenografts at the end of study.

Results: We observed that all three xenografts models investigated had mildly acidic pHe (6.74 – 6.85) (Figure A). For Granta519 xenografts, the pHe decreased significantly from week 1 to week 3 of monitoring (pH 6.82 – 6.74, p-value = 0.02). There was no significant trend in spatial heterogeneity and growth rate for any of the three xenografts models. The Ramos tumors were statistically less spatially heterogeneous than Raji and Granta519 tumors (p-value < 0.006). Granta519 and Ramos xenografts did not show correlation of contrast agent uptake with tumor growth. However, as the Raji tumor became larger, the % contrast uptake increased (C, D and E). As shown in F and G, the % contrast agent uptake correlates with ex vivo VEGF-A score (r = 0.822).

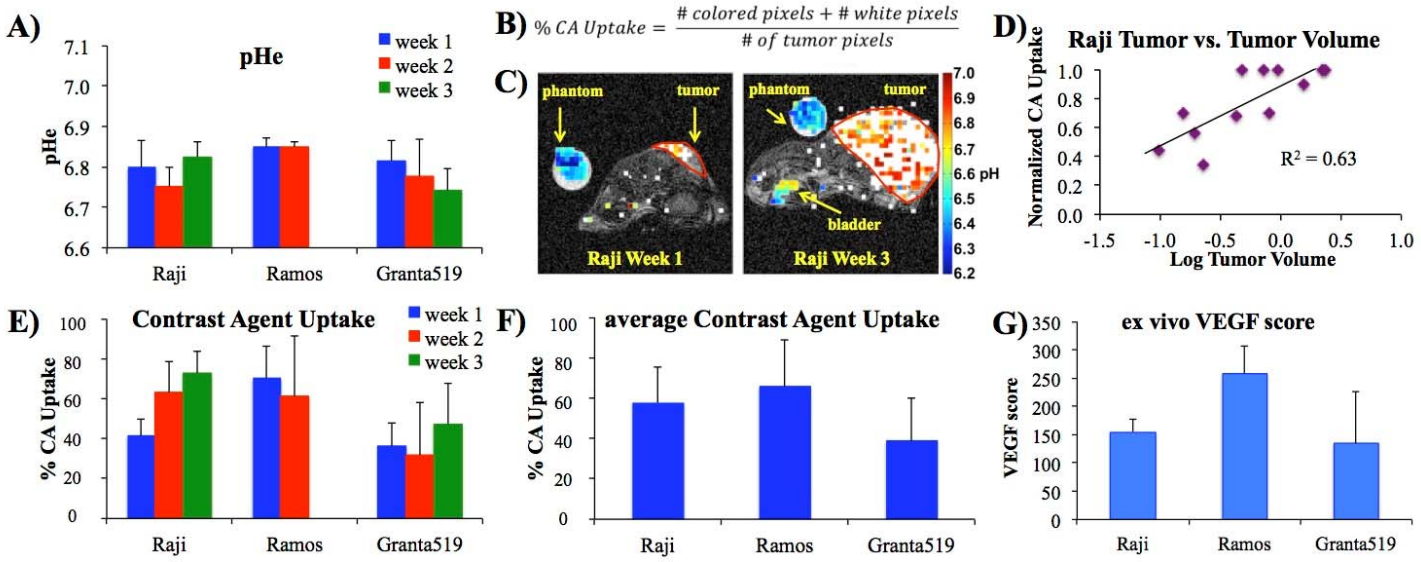

Figure 1. A) The average pHe for each individual week. **B)** Equation used to calculate CA uptake. **C)** Pixel-wise pHe map for Raji xenograft on week 1 and week 3. **E)** The average % CA uptake for each individual week, **F)** Average % uptake over 3 weeks, **G)** Semiquantitative immunoreactivity scores stained for VEGF for lymphoma xenografts Raji, Ramos and Granta519. Error bars S.D. for average measurements.

Discussion: acidoCEST MRI using Iopromide as contrast agent can be used as a molecular imaging biomarker to measure pHe of the tumor, evaluate spatial heterogeneity and % contrast agent uptake. Our method has strong clinical translation potential because it uses low saturation powers, incomplete saturation, and a clinically approved contrast agent.

References: 1) Gillies RJ, et al., Cancer Met Rev 2007, 26:311-317. 2) Chen, et al., Magn Reson Med, 2013. 3) Sheth VR, et al., Contrast Media Mol Imaging 2012, 7 26–34.