Assessing Response to Therapy Using Simultaneous PET/MRI in a Preclinical Model of Pancreatic Cancer

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INTRODUCTION

^{18}FDG PET is an outstanding method for evaluating response to anti-tumor therapy by monitoring glucose uptake. More recently, acidoCEST MRI has been shown to evaluate drug response by measuring tumor extracellular pH (pHe) caused by lactic acid production.[1] The combination of these two methods can potentially provide a more comprehensive analysis of a drug effect on the glycolysis pathway. We performed simultaneous PET/MRI studies on a mouse model of pancreatic cancer treated with metformin to explore the synergy between these two robust molecular imaging modalities.

METHODS

MR Imaging. MRI studies were performed with a CEST-FISP MRI acquisition protocol.[2] The following FISP acquisition parameters were used: TR= 3.7 ms; TE= 1.6 ms; NEX= 1.0; excitation pulse angle= 15°; slice thickness= 1.0 mm; FOV= 6.4 cm^2; 0.5 mm^2 in-plane resolution; matrix= 128 x 128; centric encoding order; unbalanced "FID" mode; 393 ms scan time.

The saturation period consisted of the following parameters: a 3.0 second continuous wave radio frequency (RF) block pulse with no additional spoiling, fat saturation pulses or respiration gating; 3.0 µT saturation power and 40 saturation frequencies ranging from -11 to 11 ppm with four ranges: -11 to -3 ppm (5 frequencies); -2.5 to 2.5 ppm (11 frequencies); 2.7-9 ppm (22 frequencies); and 10-11 ppm (2 frequencies).

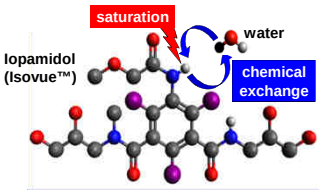
We performed a multi-slice, spin echo MRI acquisition to localize flank tumor. We then obtained a spectrum of endogenous CEST signals after acquiring four pre-injection acidoCEST MRI scans (using the parameters above) in a total scan time of 13 min. One minute of baseline scans were completed before a 200 µL bolus of Iopamidol (370 mgI/mL) was immediately administered IV and an infusion pump was connected to the catheter line to deliver the agent at 400 µL/h for the remainder of the scan. Six post-injection acidoCEST MRI scans were conducted in a total scan time of 23 min.

PET Acquisition: ^{18}FDG purchased from PetNet Pharamaceuticals (Phoenix, AZ, USA) was measured using an Atomlab 300 from Biodex Medical Systems (Shirley, NY, USA). Activity was diluted with 0.9% saline and measured until 4-12 MBq (0.1-0.32 mCi) reached with 250 µL total volume. ^{18}F-FDG was intravenously (IV) injected into the mice, and the tracer uptake was allowed to circulate for 45 minutes before initiating simultaneous PET/MRI experiments. A 1 min localizer PET scan was performed to center the mice within the detectors such that the activity spans the entire axial FOV of the NuPET™ coil from Cubresa Inc. (Winnipeg, MB, Canada), prior to initiation of simultaneous 1 h (3600 s) PET and MRI acquisition.

Data Processing: All CEST MRI analysis was performed with Bloch fitting to measure concentration of agent (uptake) and extracellular pH (pHe) using custom written programs in MATLAB (version 9.1, R2016b; Natick, MA, USA). PET images were reconstructed using Ordered Subset Maximum A Posteriori One-Step Late (OSMAPOSL) iterative algorithm. Post-processing to overlay PET and MR images was performed using VivoQuant (v3.0) provided by INVICRO Imaging Services and Software (Boston, MA, USA).[3,4]

CEST MRI CONTRAST AGENT

CEST effects from iopamidol (Isovue™, Braco Diagnostics, Inc.; FDA approved contrast agent) are used to measure tissue pHe via MRI. Iopamidol has 2 types of hydrogen atoms (protons) that can be selectively **saturated**, which causes the MR signal from these protons to disappear. The saturated protons **exchange** with neighboring water molecules, **transferring** the proton saturation to water, reducing the MR signal from water.



AcidoCEST MRI

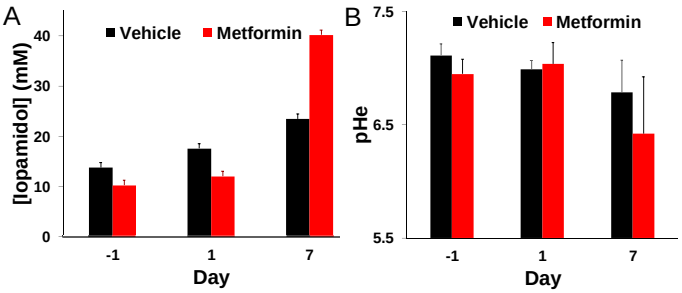


Figure 2. AcidoCEST MRI monitors tumor response to metformin. Bloch fitting estimation of iopamidol uptake (A) and tumor extracellular pH (pHe) (B) one day before initiating chemotherapy, one day after initiating therapy, and 7 days after starting therapy. An increase in agent uptake was observed for mice treated with metformin, with a statistically significant difference between Day -1 and Day 7 for metformin-treated mice ($p<0.03$), with no significant change in uptake for vehicle treated mice. A decrease in pHe ($p<0.02$) was observed for both groups of mice, with a greater decrease in average pHe observed for the metformin-treated mice. The decrease in tumor pHe in vehicle-treated mice suggested an increase in tumor metabolism as the tumor continued to grow, which is expected. *However, the greater decrease in tumor pHe after treatment with metformin was unexpected, because treatment that reduces metabolism should decrease lactic acid production and increase tumor pHe. Therefore, another test is needed to determine if metformin treatment was effective in altering tumor metabolism.*

^{18}F-FDG

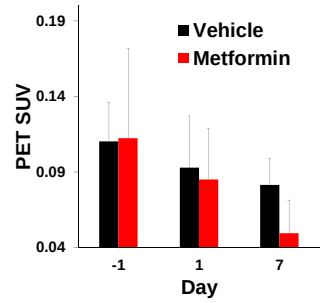


Figure 3. Comparison of ^{18}FDG uptake across the same three imaging time points for simultaneous PET/MRI. ^{18}FDG uptake decreased over the course of vehicle treatment ($p<0.01$), and metformin treatment ($p<0.002$), with a greater average decrease observed for metformin treatment. The decrease in ^{18}FDG uptake in both groups suggested a decrease in overall tumor metabolism, with a greater decrease in the metabolism of metformin-treated tumors. *Therefore, the ^{18}FDG results show that the decrease in tumor pHe measured with acidoCEST MRI was NOT due to increased metabolism, and therefore must be due to a decrease in aerobic respiration due to metformin, which caused an increase in glycolysis which increased lactic acid production.* These results show the synergy of using PET and MRI to evaluate drug response.

CEST MRI ANALYSIS WITH BLOCH FITTING

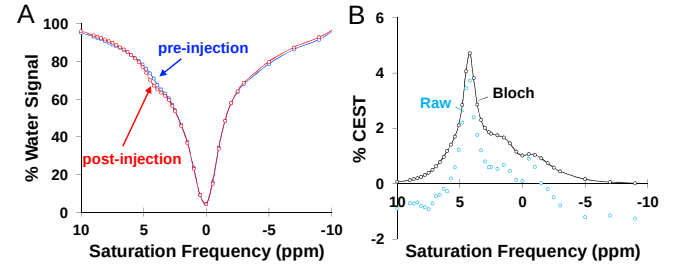


Figure 4. Example of CEST MRI analysis. Representative z-spectra are shown (**A**) to depict the change in contrast before and after injection of 0.5 M iopamidol. Bloch fitting is performed on the raw CEST data (**B**). The Bloch fitting process is modified to include pH as a fitting parameter.

SIMULTANEOUS PET/MRI

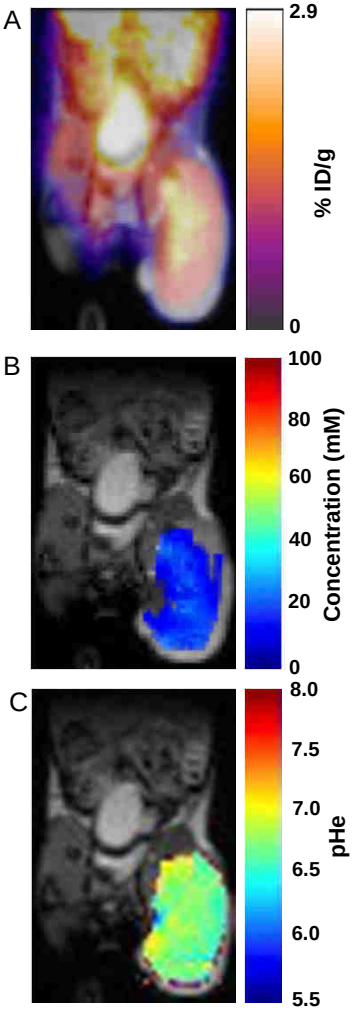


Figure 4. Representative mouse for post-processed image overlays. PET/MR image overlay (**A**) for a mouse imaged during time point two (one day after metformin treatment). Bloch fitting was performed to estimate agent uptake (**B**) and pH maps (**C**). The uptake concentration of the tumor was calculated to be approximately 20 mM, and the pH calculations show mild acidosis around pHe 6.9.

CONCLUSIONS

This study demonstrated that simultaneous PET/MRI improves interrogation of tumor glycolysis. The decrease in pH was surprising because metformin reduces overall tumor metabolism, thereby reducing lactate production.[4] If we only performed acidoCEST MRI, we would have erroneously concluded that the drug enhanced metabolism. The addition of ^{18}FDG avoided this interpretation. Similarly, if we had only performed ^{18}FDG studies, we would not have been able to identify the role of metformin on the full glycolysis pathway.

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