Oncologists Say Use This Trick: Assessing Cancer Therapeutic Efficacy *In vivo* Using [$^2H_7$]Glucose Deuterium Metabolic Imaging

Mario C. Chang,[1] Rohit Mahar,[2] Marc McLeod,[3] Anna Rushin,[1] Vinay R. Malut,[1] Geraldine L. Pierre,[1] Indu R. Malut,[1] Stephen J. Staklinski,[4] Max E. Glanz,[1] Mukundan Ragavan,[6] Gaurav Sharma,[1] Aparna D. Rao,[7,8] Brian K. Law,[5] Michael S. Kilberg,[1] James H.P. Collins,[9] Vikram D. Kodibagkar,[10] James A. Bankson,[11] Ralph J. DeBerardinis,[3,12,13] and Matthew E. Merritt[1]

[1]Department of Biochemistry and Molecular Biology, University of Florida College of Medicine, Gainesville, FL, 32610, USA | [2]Department of Chemistry, Hemvati Nandan Bahuguna Garhwal University (A Central University), Srinagar Garhwal, Uttarakhand, 246174, India | [3]Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, TX, 75390, USA | [4]School of Biological Sciences, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 11724, USA | [5]Department of Pharmacology and Therapeutics, University of Florida College of Medicine, Gainesville, FL, 32610, USA | [6]Department of Structural Biology, St. Jude Children's Research Hospital, Memphis, Tennessee, 38105, USA | [7]Peter MacCallum Cancer Centre, Melbourne, Victoria 3000, Australia | [8]Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, Victoria 3010, Australia | [9]National High Magnetic Field Laboratory, University of Florida, Gainesville, FL, 32610, USA | [10]School of Biological and Health Systems Engineering, Arizona State University, Tempe, AZ, 85281, USA | [11]Department of Imaging Physics, The University of Texas MD Anderson Cancer Center, Houston, TX, 77030, USA | [12]Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX, 75390, USA | [13]Children's Medical Center Research Institute, University of Texas Southwestern Medical Center, Dallas, TX, 75390, USA

INTRODUCTION

Metabolic imaging is a powerful tool for the visual assessment of metabolism inside the human body. Current imaging methods can be improved by increasing metabolic contrast in a safe manner. The gold standard of metabolic imaging is 2-[^{18}F]fluorodeoxyglucose-positron emission tomography (FDG-PET). FDG-PET is radioactive and restricted to a reporting of glucose uptake and retention without downstream metabolic information. Deuterium magnetic resonance imaging (DMRI) with [6,6'-$^2H_2$]glucose is nonradioactive and can generate tumoral metabolic contrast. Here, we hypothesized that assessing deuterated water (HDO) production from [$^2H_7$]glucose might further strengthen metabolic contrast and allow for tumor detection and treatment monitoring. A novel imaging platform was developed and used to distinguish baseline tumors, tumors treated with vehicle control or acute anti-glycolytic therapy, and contralateral healthy tissue. Treated tumors generated the least ^2H-signal and HDO. This approach highlights HDO as a marker of tumoral glucose utilization and indicates translational capability in humans as a safe, noninvasive, and suitable means for serial monitoring.

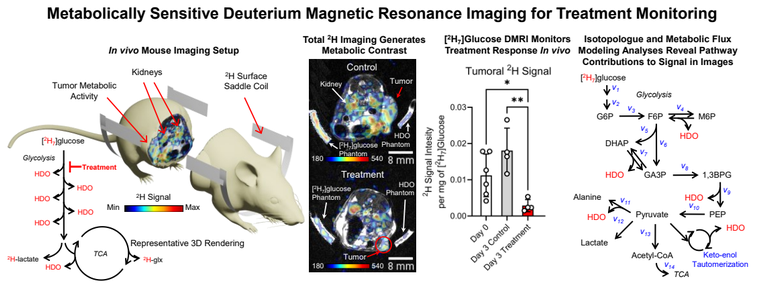


Figure 1. Utilizing deuterium metabolic imaging with [$^2H_7$]glucose to assess tumoral glucose utilization kinetics and treatment efficacy over time

Hypothesis: the production of partially deuterated water (HDO) from [$^2H_7$]glucose may lead to enhanced metabolic contrast of tumoral metabolism. 1D spectroscopy and ^2H signal imaging with gradient recalled echo can allow for a comprehensive assessment of tumoral glucose utilization and treatment efficacy. Flux modeling can reveal specific pathway contributions to HDO production.

METHODS

Yale university mouse melanoma (Yumm1.7) cell glucose utilization kinetics were characterized with ^2H NMR and GC-MS analysis.

All experimental procedures were approved by the University of Florida Institutional Animal Care and Use Committee. C57BL/6J mice were subcutaneously injected with 50,000 Yumm1.7 cells in the right flank. At 10 mm diameter, mice were entered into the study and imaged to establish a baseline. Mice were treated with vehicle control or BRAFi and MEKi therapy for 3 days followed by a final imaging session.

Imaging sessions: animals were anesthetized using isoflurane inhaled anesthetic (5%), tail vein catheterized and inserted into the MRI scanner. Animals were injected with 1.95 g/kg [$^2H_7$]glucose dissolved in heparinized (5%) saline.

Animal experiments were performed on an 11.1 T Magnex magnet (Magnex Scientific Ltd.) interfaced to a Bruker Avance III HD console running on ParaVision 6.0.1 (Bruker Instruments, Billerica, MA). Mestrenova was utilized for data analysis.

RESULTS

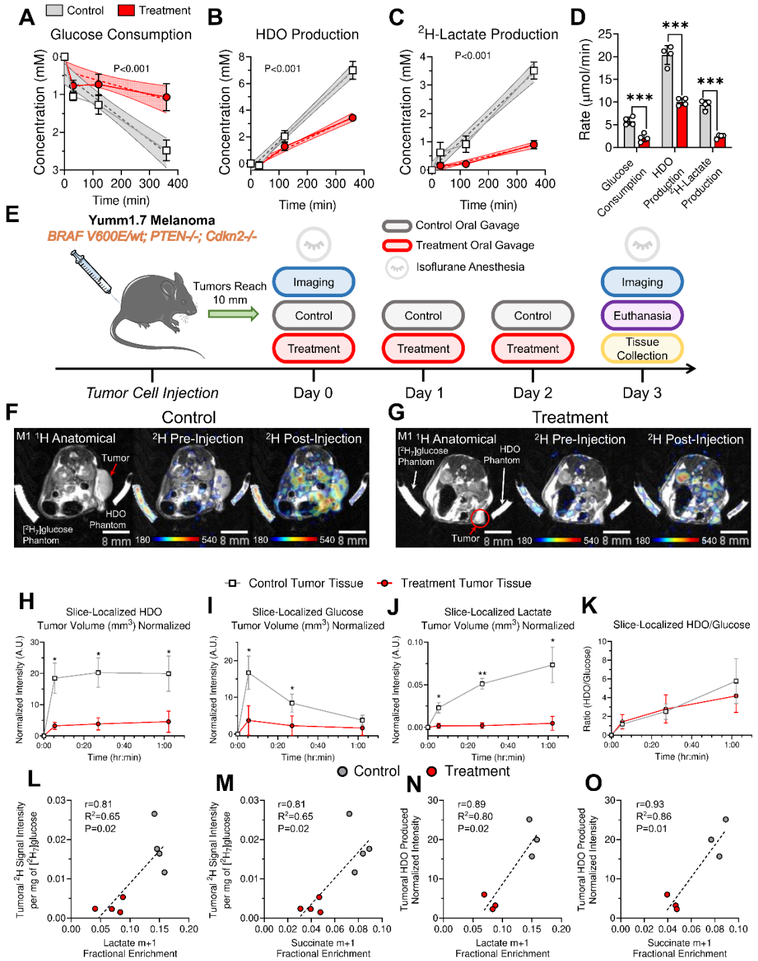
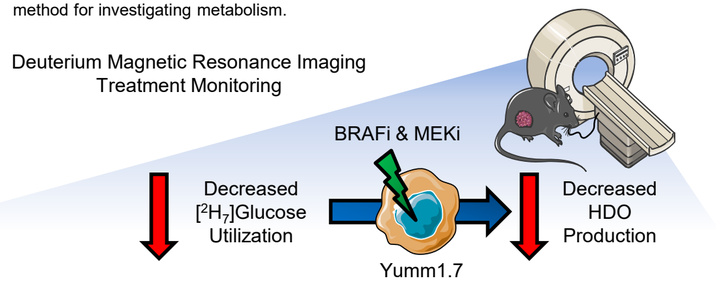


Figure 2. ***In cellulo*** **characterization of [$^2H_7$]glucose utilization and** ***in vivo*** **deuterium metabolic imaging and spectroscopy of glucose consumption and HDO production can monitor treatment.**

CONCLUSIONS

- Imaging ^2H signal and spectroscopically measuring HDO production after [$^2H_7$]glucose administration can generate tumoral metabolic contrast.
- Unlike PET-based scans, this reveals information about both uptake and consumption of glucose through HDO and ^2H-lactate production, as well as downstream metabolite labeling.
- Furthermore, this can be used to investigate the extended kinetics of glucose metabolism of an intact tumor.
- Metabolic flux modeling allowed for robust measures of glycolytic pathways and downstream metabolism.
- This work has translational capability in humans as a safe, noninvasive, and nonradioactive method for investigating metabolism.



CONTACTS

Mario C. Chang
Email: marioc14@ufl.edu

Matthew E. Merritt
Email: matthewmerritt@ufl.edu

REFERENCES

1. R. L. Siegel, A. N. Giaquinto, A. Jemal, Cancer statistics, 2024. CA A Cancer J Clinicians 74, 12–49 (2024).
2. H. M. De Feyter, K. L. Behar, Z. A. Corbin, R. K. Fulbright, P. B. Brown, S. McIntyre, T. W. Nixon, D. L. Rothman, R. A. de Graaf, Deuterium metabolic imaging (DMI) for MRI-based 3D mapping of metabolism in vivo. Science Advances 4, eaat7314 (2018).
3. M. S. Linet, T. L. Slovis, D. L. Miller, R. Kleinerman, C. Lee, P. Rajaraman, D. A. B. Gonzalez, Cancer Risks Associated With External Radiation From Diagnostic Imaging Procedures. 62, 75–100 (2012).
4. K. Meeth, J. X. Wang, G. Micevic, W. Damsky, M. W. Bosenberg, The YUMM lines: a series of congenic mouse melanoma cell lines with defined genetic alterations. Pigment Cell Melanoma Res 29, 590–597 (2016).