

Multimodal Non-Invasive Imaging of Tumor Hypoxia and Metabolism using EPR Oxygen Imaging and Hyperpolarized

¹³C-MRI

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Summary

Human tumors exhibit a variety of abnormal phenotypes such as altered metabolic status, compromised vasculature resulting in hypoxia, and micro-environmentally mediated changes in gene expression. Many tumor types can undergo aerobic glycolysis, known as the Warburg effect where tumors can abnormally obtain as much as 50% of their energy (ATP) by metabolizing sugar glucose directly to lactate even in the presence of oxygen. Likewise, based on invasive oxygen electrode measurements of human tumors, approximately one half of tumors of a given histology exhibit marked hypoxia prior to therapy. Collectively, these traits can contribute to resistance to cancer treatments including radiation and chemotherapy. Non-invasive assessment of altered tumor metabolism and tissue hypoxia might be useful for both diagnostic and treatment strategies. In this study electron paramagnetic resonance imaging (EPRI), a sensitive method to non-invasively map tumor oxygenation, and hyperpolarized MRI of ¹³C-labeled pyruvic acid, which can provide a measure of energy metabolism, are coupled to determine the relationship between these important physiologic parameters.

Method

3D oxygen imaging in Squamous Cell Carcinoma (SCC) bearing mouse leg was performed using a homebuilt 300 MHz time-domain EPR imager with the single point imaging (SPI) sequence. As EPR imaging, the mouse was transferred to 4.7T or 7T MRI scanner with the common RF coil assembly. After anatomical ¹H images were obtained, typical ¹³C Magnetic Resonance Spectroscopic Imaging (MRSI) was performed after administration of hyperpolarized [¹⁻¹³C]-pyruvic acid.

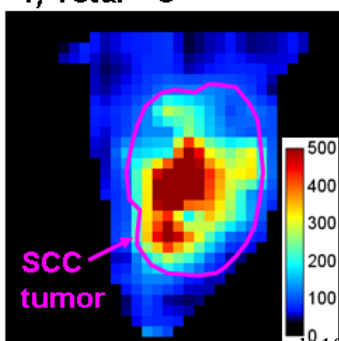
Results

EPR oxygen imaging showed that there were hypoxic and relatively well oxygenated regions in the SCC tumors. Percentage of hypoxic (< 10 mmHg) fraction increased with tumor growth. Sequential hyperpolarized ¹³C MRSI revealed that 1) high pyruvate but low lactate peaks were observed in normal muscle region. 2) Some well oxygenated tumor regions showed high lactate and pyruvate peaks. 3) High lactate but small pyruvate peaks were observed in hypoxic regions. Totally, a mild negative correlation was observed between tumor pO₂ level and lactate production or lactate/pyruvate ratio. These results suggests that EPR oxygen imaging combined with hyperpolarized ¹³C MRSI confers the opportunity for better understanding on the relationship between tumor hypoxia and energy metabolism in non-invasive manner.

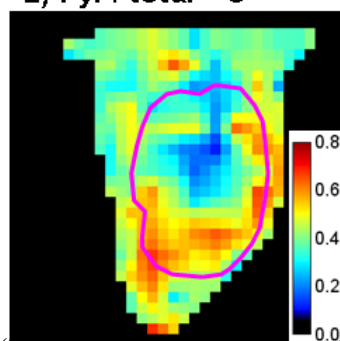
Reference

Matsumoto S. et al. *J. Clin. Invest.* 2008, 118(5):1965-73

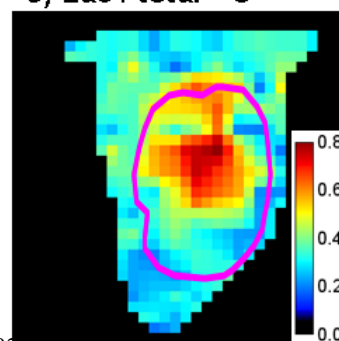
1) Total ¹³C



2) Pyr / total ¹³C



3) Lac / total ¹³C



4) pO₂ (mmHg)

