Imaging Oncogene Expression Using Hyperpolarized Succinic Acid

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Purpose: The objective of this work was to overcome inherent insensitivity of *in vivo* MR by demonstrating metabolic imaging of the Succinate Dehydrogenase oncogene expression. This was accomplished by imaging the products of Krebs Tricarboxylic Acid Cycle *in vivo* using PHIP (Parahydrogen Induced Imaging) modality of hyperpolarization in real time in tumor bearing mice. A recent discovery which has revived interest in the TCA cycle of cancer cells is the "succinate oncogene", an isoform of the standard TCA cycle enzyme succinate dehydrogenase (SDH). This oncogene originally defined in rather rare tumors is now believed to be prevalent and to activate Hypoxia Inducing Factor -HIF1α by the mechanism shown in Fig. 2. Hypoxia contributes significantly to the pathophysiology of major categories of human disease, including myocardial and cerebral ischemia, cancer, pulmonary hypertension, congenital heart disease and chronic obstructive pulmonary disease.

Materials and Methods: ^{13}C deuterated fumarate was hydrogenated by parahydrogen and rhodium-catalysis to 1-^{13}C succinate and hyperpolarized by PHIP to 8±2% before tail-vein injection into tumor-bearing BALB/c mice.

Results: After injection of hyperpolarized 1-^{13}C succinate hyperpolarized metabolic products were detected with 20,000 fold increased sensitivity for *in vivo* ^{13}C imaging and spectroscopy over 3 – 5 minutes. The metabolic fate of hyperpolarized ^{13}C succinate differed in two tumor populations: in RENCA renal carcinoma metabolic products malate C1 and C4,fumarate C1, glutamate C1 and citrate C6 (N = 10) were defined (Fig.1); and in Lymphoma A20 the hyperpolarized metabolic products were limited to ^{13}C malate C1 and C4. HIF1α expression in different subcutaneous tumor models in BALB/c mice (Fig.3). Nuclear staining present in lymphoma A20 (left) is absent in RENCA (right) indicative of significant HIF1α expression only in lymphoma A20 (Fig.4). Positive control followed the convention using an example of human glioblastoma (not shown) which stained heavily for HIF 1α.

Fig. 1. RENCA renal cancer

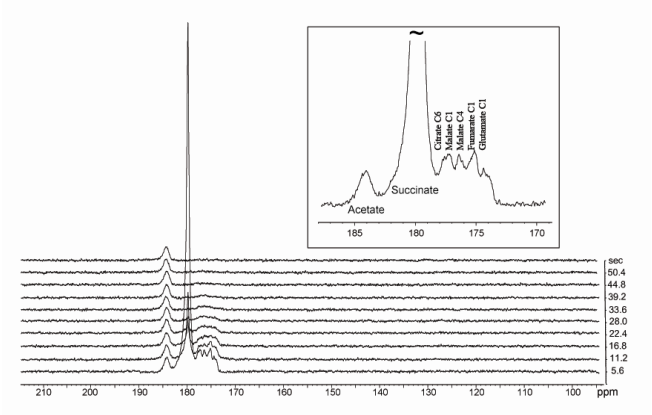


Fig. 2.

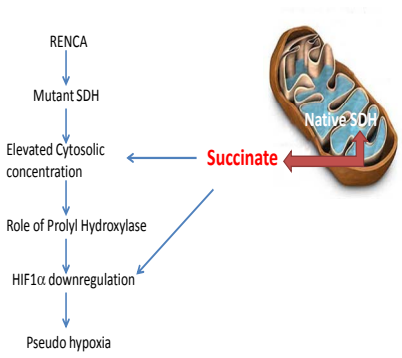


Fig.3. Lymphoma A20

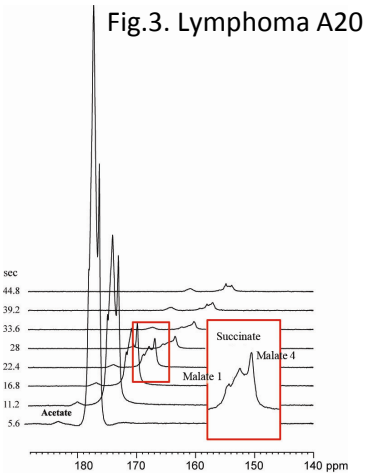
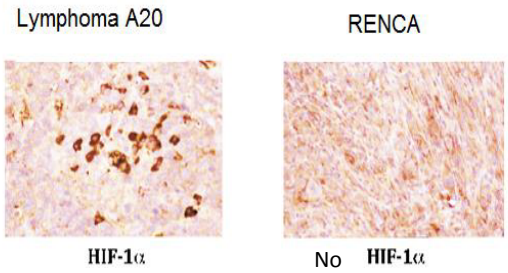


Fig. 4.



Conclusion: Hyperpolarized succinate may interrogate different steps of TCA cycle metabolism and can image the SDH oncogene expression in real time.

References:
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