Characterization of Biosynthetic Lactate Metabolism in Cancer

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Introduction

Metabolism is a critical factor that is required for tumor survival and tumorigenicity. One of the hallmarks of cancer metabolism is enhanced glucose uptake and its conversion to lactate despite the presence of available oxygen,[1] resulting in the generation of ATP for energetics through glycolysis and contribution to biosynthesis required for proliferation.[2,3] Apart from glycolysis, oxidative phosphorylation (OXPHOS) is a source for tumor energetics that is required for dormant tumor cells to survive a shutdown of oncogenic signaling pathways and glycolysis, thus resulting in disease relapse.[4] Lactate secreted from glycolytic cells is metabolized in the mitochondria of aerobic OXPHOS cells resulting in ATP.[5] This finding proposes a new model for tumor metabolism where glycolytic and OXPHOS compartments within a tumor work together to maximize energy sources necessary to survive (metabolic symbiosis model)[6] (Fig. 1). Our goal is to model lactate oxidation and incorporation into biosynthetic pathways in cancer. We will use various types of analytical tools, including solid-state NMR spectroscopy, to validate a novel, clinically-available positron emission tomography (PET) imaging agent, 3-[^{11}C] lactate, to image metabolic symbiosis in tumors.

Experimental

Utilized for our experiments is the NHMFL's 800 solid-state NMR spectrometer that is operational with Bruker Avance HD console and is equipped with a homebuilt 3.2 mm MAS probe. ^{1}H-^{13}C cross-polarization magic-angle spinning (CPMAS) method developed in solid-state NMR spectroscopy was utilized for the analysis of cell metabolites that have been enriched with U-[^{13}C] lactate and U-[^{13}C] glucose. Our ultimate samples for analysis will be tissues from mice that have been injected with 3-[^{13}C] lactate. Following the injection of 1 µmol 3-[^{13}C] lactate, mice will be sacrificed after 30 minutes, tissues harvested, and flash frozen. Tissues will be lyophilized for sampling in MAS rotors for solid-state NMR experiments.

Results and Discussion

Fig. 1 shows ^{1}H-^{13}C CPMAS solid-state NMR spectra measured on the metabolites of cell lines enriched with U-[^{13}C] lactate and U-[^{13}C] glucose. The U-[^{13}C] glucose spectrum was acquired as an additional control to determine the difference between the glucose and lactate metabolic pathways. In the next step we will proceed to analyze tissues from mice that have been injected with 3-[^{13}C] lactate to measure and measured with solid state MAS NMR for analyzing lactate incorporation into metabolite classes. Our solid-state NMR data will be combined with solution-state NMR and mass spectrometry data for a targeted analysis of pathways including TCA cycle and key amino acids.

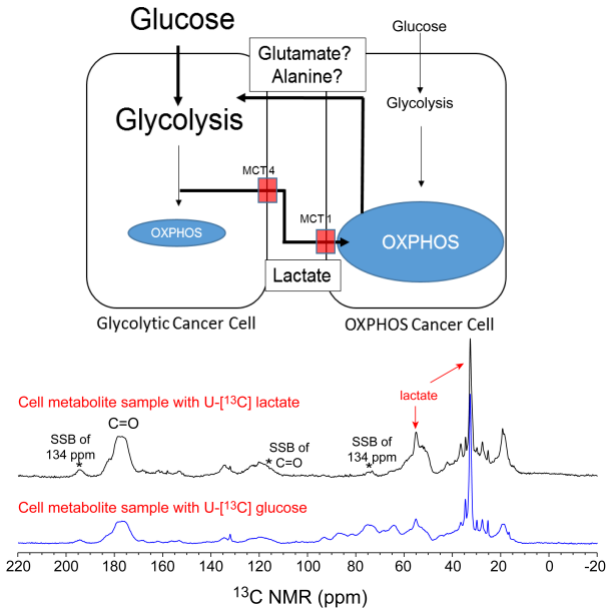

Fig.1 Proposed metabolic symbiosis model in cancer and solid-state ^{1}H-^{13}C CPMAS NMR spectra of cancer cell metabolites obtained from [U-^{13}C]-labeled lactate and glucose. MCT: monocarboxylate transporter.

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References

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