Characterization of Biosynthetic Lactate Metabolism in Cancer

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Introduction

The cancer cell metabolism involves glycolysis and oxidative phosphorylation (OXPHOS) for tumor energetics and proliferation.[1,2] Glycolysis generates ATP and OXPHOS is required for dormant tumor cells to survive a shutdown of oncogenic signaling pathways and glycolysis.[3] Thus, a monitor of OXPHOS could be used to quantitate viable tumor, and drugs that target OXPHOS could be used to ablate tumor. The goal of this work is to model lactate oxidation and incorporation into biosynthetic pathways in cancer. We are to use solid-state NMR spectroscopy to investigate the downstream metabolites of lactate in tumors after adding of U-[$^{13}C_3$] lactate to an aggressive, castrate resistant prostate cancer cell line. We identify time-dependent uptake in tumor as well as other organs including brain. This information will not only allow us to model the tracer, necessary for quantitative analysis of in vivo metabolism, but will give us important information about the *in vivo* fate of lactate in OXPHOS metabolism.

Experimental

Samples for analysis will be cell lines with a spectrum of aggressive features that produce lactate for 24 hours. We have added U-[^{13}C]-labeled Glu-Gln, Glu-Ala, Glu-Lac, and Glu-Tyr to the cell lines to determine differences between glucose and lactate metabolic pathways. Solid-state ^{13}C spectra were measured for the resultant metabolites by employing ^{1}H-^{13}C cross-polarization magic-angle spinning method.

Results and Discussion

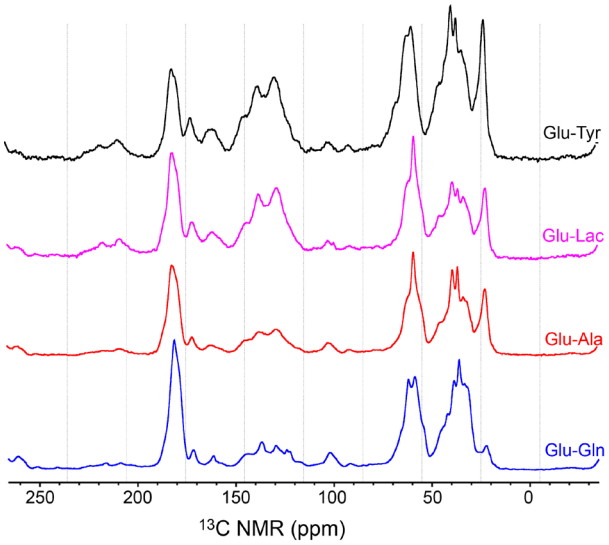

Fig.1 ^{1}H-^{13}C cross-polarization magic-angle spinning (CPMAS) spectra of cancer cell metabolites.

Figure 1 shows the ^{1}H-^{13}C CPMAS NMR spectra of cancer cell metabolites of U-[^{13}C]-labeled Glu-Gln, Glu-Ala, Glu-Lac, and Glu-Tyr. These materials are resulting from aerobic glycolysis and the oxidative phosphorylation (OXPHOS) processes in cancer cells. Although the various spectra shown in Figure 1 are all very similar, looking at each spectrum shows a difference in small peaks, and also the peak pattern in each case shows a difference in the relative peak intensities. We believe that by monitoring the NMR spectra of cell metabolites we will be able to understand the metabolic pathways involved in cancer cells.

Conclusions

Cancer cell metabolites of U-[13C] Glu-Gln, Glu-Ala, Glu-Lac, and Glu-Tyr have demonstrated not only a similar pattern in their ^{1}H-^{13}C CPMAS spectra but the differences in the minor peak positions as well as in the relative peak intensities.

Acknowledgements

The National High Magnetic Field Laboratory is supported by the National Science Foundation through NSF/DMR-1157490/1644779 and the State of Florida.

References

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[3] Viale, A., *et al.*, Nature, **514(7524)**, 628-532 (2014).