PERFUSION CORRELATED HETEROGENEITY IN NSCLC PATIENT TUMOR GLUCOSE METABOLISM

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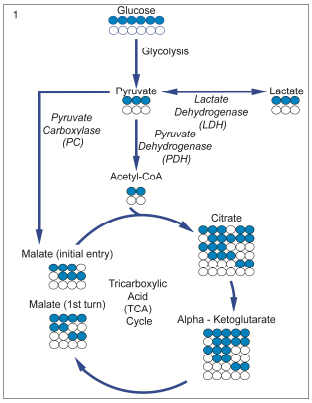
Target Audience

Researchers interested in cancer metabolism, tumoral heterogeneity, metabolite-based PET analogs, and/or advanced imaging methods of perfusion assessment and the correlations between these parameters in primary human tumors.

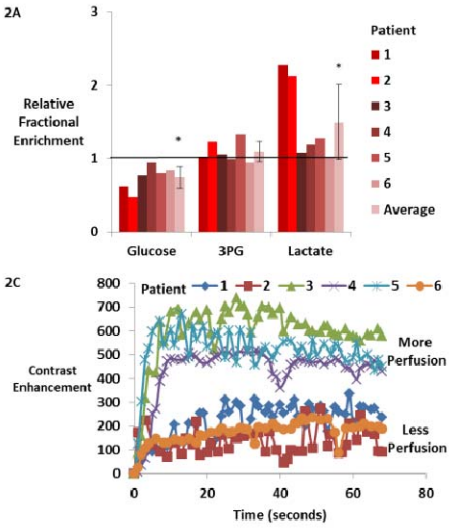


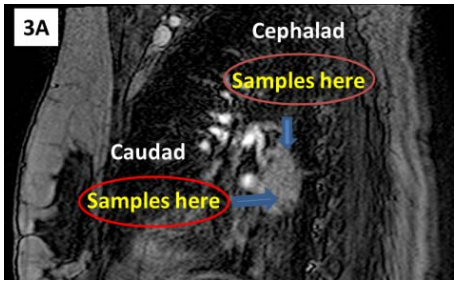
Purpose

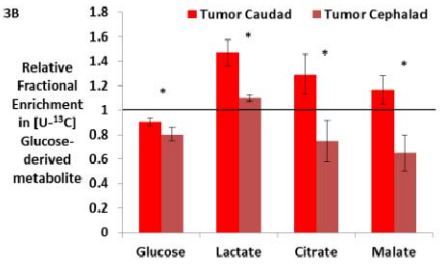
In vivo explorations in spontaneously-formed human tumors of the magnitude and scales of metabolic heterogeneity are fairly sparse. The "Warburg Effect," an enhancement of conversion of glucose into lactate upon cellular transformation, is thought to be a hallmark of malignancy and the molecular basis of the clinical utility of FDG-PET to detect tumor tissue. However, empirical evidence validating the Warburg Effect *in vivo* in spontaneously-formed FDG-PET positive human tumors, and exploring the relationship between both inter- and intratumoral heterogeneity in tumor glycolysis and other aspects of metabolism or tumor biology such as perfusion, is fairly sparse. A multitude of phenotypes in cancer metabolism are being submitted as therapeutic targets in model systems. Therefore, establishing a framework in one of the field's most well understood metabolic phenotypes in model systems of how to conduct *in vivo* metabolic assays in patients and subsequently sample tissue, and finally correlate metabolism to other aspects of tumor biology in a manner that can account for metabolic heterogeneity could potentially serve as a guide to future clinical and basic studies in primary human tumors for more nascent phenotypes.

Experimental Methods

Here we report a clinical study in early-stage non-small cell lung cancer (NSCLC) incorporating pre-operative imaging and [U-^{13}C] glucose infusions prior to lobectomy, followed by metabolic analysis of tumor and non-cancerous lung. The pre-operative imaging method discussed is Dynamic Contrast Enhanced (DCE) MRI. Tissue samples were resected in the operating room and immediately frozen in liquid nitrogen for subsequent metabolic analysis. In each patient, resected tissue samples were analyzed for ^{13}C enrichment in metabolites of the pathways in Figure 1 by the complimentary methods of GC-MS and NMR.







Results and Discussion

At the intertumoral scale, tumor glycolytic enhancements relative to non-cancerous lung ("relative fractional enrichment" as determined by GC-MS) were highly variable in magnitude (Figure 2A). Additionally, these glycolytic enhancements were directly correlated to glucose-derived TCA cycle activity (as assessed by citrate M+2 by GC-MS), potentially providing evidence in contrast to "switch" models from oxidative glucose metabolism to glycolysis upon transformation (Figure 2B). Suprisingly, glucose-derived TCA cycle activity, as assessed by both GC-MS fractional enrichment and NMR via glutamate C4, was inversely correlated with pre-operative perfusion assessed as time to and value of maximum contrast enhancement of the DCE-MRI scan (Figure 2C,2D). Finally, we provide GC-MS evidence for regional intratumoral heterogeneity in glucose metabolism (Figure 3A,B). (* = $p<0.05$, paired t-tests in 2A and 3B, pearson's correlation coefficient in 2B, two sample equal variance t-test in 2D).

Conclusions

These results necessitate considerations of tumoral metabolic heterogeneity during experimental design in the field of cancer metabolism of basic and translational studies in primary human tumors. Microenvironment-based pre-operative imaging may assist in consistent sampling decisions in comparing tumors. In NSCLC, perfusion may be a significant determinant of both oxidative and non-oxidative glucose-derived metabolism.