Characterization of Lactate Metabolism in Neuroendocrine Prostate Cancer

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Background

Neuroendocrine Prostate Cancer (NEPC) is an aggressive form of prostate cancer that is invariably lethal and resistant to conventional therapy. Although the complex molecular mechanisms driving this aggressive phenotype remain to be elucidated, we are investigating (i) the role of enhanced nutrient utilization and energetics and (ii) the effects of the tumor microenvironment on nutrient utilization as drivers for this phenotype. We are developing a model for metabolic crosstalk in NEPC (*i.e.* the metabolic symbiosis model) where lactate produced by hypoxic, glycolytic cells can be utilized by adjacent normoxic cells engaged in OXPHOS. Based upon our extensive experience in NEPC metabolism we hypothesized that lactate is an important nutrient by which NEPC cells enhance biomass and survival through mitochondrial function.

Methods

The Prostate Neuroendocrine Cancer (PNEC) cell line derived from the CR2-TAg transgenic mouse model for NEPC was used. [^{13}C] lactate labeling studies were performed in nutrient-defined DMEM-F12 media with dialyzed serum and added to cells for 24 hours under conventional culture conditions. Gas chromatography/mass spectrometry (GC/MS) was used to measure isotopologue levels of lactate metabolites in PNEC cells. Non targeted tracer fate detection software was used to identify downstream metabolites of [^{13}C] lactate in PNEC cells. Cell viability was assessed with sulforhodamine B staining, a validated viability assay independent of cellular metabolism.

Results

Lactate is metabolized in the TCA cycle of PNEC cells. We identified hundreds of metabolites from multiple classes (e.g. sugars, amino acids, lipids, and unknowns) that are products of imported lactate. We specifically identified that lactate is metabolized into "oncotransmitters" (glutamate and GABA) that have roles in PNEC cell signaling. Moreover, lactate enhances PNEC cell viability in the absence of glucose that exceeds that of other well-characterized nutrients pyruvate and acetate.

Conclusions

We have successfully identified that lactate is a source for energy and biomass in PNEC cells. Metabolism of lactate through the TCA cycle results in the production of multiple classes of metabolites such as sugars, amino acids, lipids, and unknowns. Moreover, the ability of lactate to rescue PNEC cells from glucose deprivation may exceed that of characterized substrates including pyruvate and acetate.

Conflict of Interest

None

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