Unique Central Carbon Metabolism in Small Cell Prostate Cancer

Zhepeng Wang[1,2], Jan R. Crowley[3], John K. Lee[4,5], and Joseph E. Ippolito[1,2]

[1]Mallinckrodt Institute of Radiology, [2]Department of Genetics, [3]Mass Spectrometry Research Resource, Washington University in St Louis School of Medicine, [4]Division of Hematology and Oncology, Department of Medicine, [5]Institute of Urologic Oncology, Department of Urology, David Geffen School of Medicine at UCLA

Background

Small cell neuroendocrine prostate cancer (SCPC) 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 hypothesize that small cell carcinomas have higher "metabolic plasticity" than adenocarcinomas, allowing them to use alternative nutrients more efficiently, thus enhancing their ability to survive stresses. Here, we demonstrate through transcriptomics and metabolomics that small cell prostate carcinomas have enhanced central carbon metabolism that allows them to metabolize unique nutrient sources necessary to maintain viability.

Methods

RNASeq data were obtained from the Beltran et al. datasets [*Nat Med.* 2016 Mar;22(3):298-305]. Multiple prostate cancer cell lines representing both adenocarcinomas and small cell carcinomas including LNCaP, DU145, IGR-CaP1, PC3, LASCPC-01, and PNEC were used. All experiments were performed in nutrient-defined media with dialyzed serum. Targeted [^{13}C] metabolic flux studies were performed using labeled nutrients added to cell culture and subsequently analyzed with gas chromatography/mass spectrometry (GC/MS). Targeted metabolomics of central carbon metabolism were performed with liquid chromatography/mass spectrometry (LC/MS). Solution state [^{1}H] and [^{13}C] NMR studies were performed on cell lysates and media. Cell viability was assessed with sulforhodamine B staining.

Results

Transcriptome analyses demonstrated that genes involved in central carbon metabolism were sufficient to segregate patients with castrate resistant prostate adenocarcinoma (CRPC-Adeno) from castrate resistant neuroendocrine prostate cancer (CRPC-NE). Nutrient deprivation studies demonstrated that under normoxic conditions, lactate and pyruvate as primary carbon sources enhanced the viability of multiple prostate cancer cell lines, notably PNEC, PC3 and LASCPC-01 cells. Although hypoxic conditions eliminated the beneficial effects of these metabolites as primary substrates, we identified a panel of metabolites that could serve as primary carbon sources in hypoxia and maintain viability. Metabolomic profiling and flux studies in PNEC cells further confirmed the presence of robust biosynthetic pathways in small cell carcinoma cell lines.

Conclusions

We have successfully identified that small cell prostate carcinoma cell lines can utilize various primary carbon substrates as sources of energy in both normoxic and hypoxic conditions to enhance viability. These effects are not seen in prostate adenocarcinoma cell lines, suggesting that small cell carcinomas may have enhanced ability to metabolize alternative substrates for energy in the tumor microenvironment. These findings suggest that new approaches that target nutrient consumption and metabolism may be required to enhance the efficacy of anti-tumor therapies in patients with prostate cancers with a neuroendocrine component.

Conflict of Interest

None

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