Metabolic vulnerabilities in therapy resistance in prostate cancer

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Background
Acquire resistance to targeted therapies in cancer is a rising unmet clinical need. Cellular plasticity endows cancer cells with the ability to overcome therapy by switching their cellular state. At the same time, metabolic dependencies arise in response to alterations in oncogenic growth signaling and might constitute an Achilles heel that can be exploited therapeutically. Although, a major mechanism of resistance in prostate cancer (PCa) involves the reactivation of the androgen receptor (AR) axis, increasingly potent second-generation AR inhibitors have driven an increased incidence of AR independent resistant tumors that acquire features of neuroendocrine prostate cancer (NEPC) through lineage plasticity. Therefore, our goal is to understand the mechanisms underlying lineage plasticity during NEPC differentiation in the context of PKCλ/ι deficiency, recently identified in our laboratory as a novel tumor suppressor in NEPC.

Methods
We have developed cell systems by CRISPR-CAS9 to delete PKCλ/ι and an in vivo mouse model using conditional knockout of PKCλ/ι and PTEN in a prostate epithelial-specific cre system. With these models, we investigated the role of PKCλ/ι in PCa signaling and metabolism during NEPC differentiation and validated our findings in human NEPC samples.

Results
Our data demonstrate that the loss of PKCλ/ι results in the metabolic reprogramming of PCa cells to sustain their increased proliferation and epigenetic needs, thus favoring cancer cell plasticity and NEPC differentiation. We have fully dissected the molecular mechanism of this PKCλ/ι-mediated metabolic switch, and demonstrated that PKCλ/ι loss activates an mTORC1/ATF4 driven cascade that results in the upregulation of the serine, glycine, one-carbon (SGOC) pathway, including PHGDH, the first and limiting enzyme in this biosynthetic cascade. Genetic or pharmacological blockade of the mTORC1/ATF4/SGOC axis inhibits lineage plasticity and NEPC promoted by PKCλ/ι loss. Furthermore, mTORC1/ATF4/SGOC axis is upregulated in human NEPC samples as compared to CRPC adenocarcinomas and constitutes a synthetic vulnerability of NEPC, demonstrating the clinical relevance of our findings. Serine metabolism fuels the methionine salvage pathway to produce SAM for DNA methylation. Consistently, PKCλ/ι-deficient cells also have higher intracellular levels of SAM and increased genome wide methylation. Inhibition of DNA methyltransferase with decitabine severely reduced NEPC and basal markers in PKCλ/ι KO cells, organoids and in vivo mouse xenografts.

Conclusions
Our results support a model whereby the metabolic reprogramming orchestrated by PKCλ/ι deficiency through the mTORC1/ATF4/PHGDH axis creates a vulnerability in NEPC that can be exploited therapeutically by targeting the SGOC pathway and DNA methylation.

Conflict of Interest
No competing interests.

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