879 REVERSAL OF LACTATE AND PD-1-MEDIATED MACROPHAGE IMMUNOSUPPRESSION CONTROLS GROWTH OF PTEN/P53-DEFICIENT PROSTATE CANCER

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Background There has been renewed interest in immunotherapy for the treatment of advanced prostate cancer (PC), partly based on the anti-tumor immune activation that occurs with ADT, and partly based on the clinical responses to immune checkpoint inhibitors (ICI) targeting CTLA-4 and PD-1/PD-L1 in other cancers.[1-3] However, only 10-25% of metastatic castrate-resistant prostate cancer (mCRPC) patients respond to ICI, with a lack of durable benefit in the majority of patients.[4-5] PTEN LOF alterations, which occur in approximately 50-75% of mCRPC patients, are associated with poor prognosis, development of metastases,[6-8] and immunosuppressive tumor microenvironment.[9-11] Given the aggressive natural history and poor therapeutic outcomes of PTEN-mutant advanced PC to standard-of-care hormonal therapies,[6] chemotherapies[12] and ICI,[10] a deeper understanding of immune evasion mechanisms is critical for the discovery of new therapeutic strategies to effectively treat this molecular subset of AVPC.

Methods Prostate-specific PTEN/p53-deficient genetically engineered mice (GEM) (40) were screened for autochthonous prostate tumor development and monitored for response to therapy by ultrasound and MRI, respectively. Following the development of 150-200 mm^3 solid tumors, the mice were treated with either androgen deprivation therapy (degarelix), PI3K inhibitor (copanlisib), or PD-1 antibody, as single agents or their combinations. Harvested tumors following *in vivo* treatment underwent flow cytometry, or utilized for *ex vivo* studies on single cell suspensions or sorted TAM. Single cell RNAseq on human metastatic bone and lymph node samples were performed using established methods.[13]

Results We performed co-clinical trials in prostate-specific PTEN/p53-deficient genetically engineered mice, and discovered that recruitment of PD-1-expressing tumor-associated macrophages (TAM) thwarts androgen deprivation therapy (ADT)/PI3K inhibitor (PI3Ki) combination-induced tumor control. Strikingly, we observed TAM-dependent ~3-fold increased anti-cancer response with ADT/PI3Ki/PD-1 antibody (aPD-1) combination. Mechanistically, decreased lactate production from PI3Ki-treated tumor cells suppressed histone lactylation within TAM, resulting in their phagocytic activation, which was augmented by ADT/aPD-1 treatment and attenuated by feedback activation of Wnt/β-catenin-pathway. Furthermore, single-cell RNA-sequencing analysis in mCRPC patient biopsy samples revealed a direct correlation between high glycolytic activity and TAM phagocytosis suppression.

Conclusions Our findings demonstrate that immunometabolic strategies to reverse lactate and PD-1-mediated TAM immunosuppression by PI3Ki and aPD-1, respectively, in combination with ADT, controls tumor growth and warrants further clinical investigation in PTEN/p53-deficient mCRPC.

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Ethics Approval Murine experiments were performed in accordance with NIH guidelines and protocol approved by the Institutional Animal Care and Use Committee (IACUC) at University of Chicago (ACUP 72483-12). Bone metastatic PC samples were collected and handled in accordance to the protocol approved by the Institutional Review Board (IRB, Dana Farber/Harvard Cancer Center protocol 13-416 and Partners protocol 2017P000635/PHS). For metastatic lymph nodes of PC patients, baseline biopsies were collected and processed as mentioned in the investigator-initiated, IRB-approved clinical trial (IRB-18-0154 of Chicago, NCT03572478) of rucaparib in combination with nivolumab, co-sponsored by Clovis Oncology and Bristol Myers Squibb.

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