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. 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. PTEN LOF alterations, which occur in approximately 50-75% of mCRPC patients, are associated with poor prognosis, development of metastases, and immunosuppressive tumor microenvironment. Given the aggressive nature of metastatic PC and poor therapeutic outcomes of PTEN-mutant advanced PC to standard-of-care hormonal therapies, chemotherapies, and ICI, 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 mm³ solid tumors, the mice were treated with either androgen deprivation therapy (dexamethasone, 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.

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 acetylation 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.

REFERENCES

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 (motes).2014.08.044.