831 TARGETING TUMOR OXIDATIVE METABOLISM TO OVERCOME HYPOXIA-INDUCED IMMUNOTHERAPY RESISTANCE IN PROSTATE CANCER

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Background Immunotherapy is successful in "hot" tumors with pre-existing immune infiltrates. However, "cold" tumors like prostate cancers remain unresponsive.[1,2,3] Murine prostate tumors harbor hypoxic regions, islands of immune privilege, excluding T cells while promoting recruitment and suppressive polarization of myeloid-derived suppressor cells (MDSC). Targeting hypoxia using the hypoxia-activated prodrug, TH-302 (Evofosfamide) reduced MDSC driven suppression, enhanced T cell function, improving sensitivity to immune checkpoint blockade (ICB).[4] In a Phase I clinical trial, combining Evofosfamide with Ipilimumab (anti CTLA-4) elicited both objective responses and prolonged disease stabilization in late-stage "cold" tumor patients. However, Evofosfamide reduces, but does not eliminate hypoxia and patients resistant to Evofosfamide/Ipilimumab combination exhibited hyper-metabolic tumors.[5] Targeting tumor oxidative metabolism reduced hypoxia and improved sensitivity to PD-1 blockade.[6,7] We hypothesized that targeting tumor oxidative metabolism using mitochondrial complex I inhibitors might diminish tumor hypoxia, and act synergistically with Evofosfamide to sensitize unresponsive tumors to immunotherapy. Since oxidative phosphorylation (OxPhos) is also crucial to T cell function, we tested multiple doses of two complex I inhibitors to determine a regimen with optimal capacity to compromise tumor oxygen metabolism while sparing T cell metabolic fitness.

Methods Utilizing the transplantable TRAMP-C2 prostate tumor model, we investigated the capacity of two complex I inhibitors to reduce tumor oxidative metabolism, diminish myeloid suppressive capacity and improve T cell immunity, alone and in combination with Evofosfamide and ICB. We assessed tumor burden, evaluated immune composition using flow cytometry and characterized metabolism using Seahorse XFe96 analyzer.

Results While Evofosfamide or OxPhos inhibition alone did little to inhibit prostate cancer progression, combination acted synergistically to reduce tumor burden and augment tumor-specific CD8 and CD4 effector T cell proliferation. Complex I inhibition reduced TRAMP-C2 tumor cell proliferation and MDSC suppressive polarization, but improved function of previously activated T cells. Consequently, neither prior, nor concurrent, complex I inhibition diminished efficacy of CTLA-4/PD-1 blockade in TRAMP-C2 . Used in combination, complex I inhibition and ICB promoted tumor-infiltrating T cell proliferation, activation and cytotoxicity while reducing dysfunction/exhaustion markers.

Conclusions Tumor hypoxia and associated immune suppressive programming can be reduced through both restoration of oxygen supply through vascular remodeling (i.e. Evofosfamide) and limitation of tumor oxygen metabolism (e.g. complex I inhibition). OxPhos inhibition selectively inhibits tumor and myeloid function, while sparing T cell function and responsiveness to ICB. Coordinated remodeling of tumor oxygen metabolism with existing drugs can compromise hypoxia-associated T cell suppression without compromising intrinsic T cell metabolic potential.

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