DISRUPTED OXYGEN SUPPLY AND TUMOR HYPER-OXYGEN CONSUMPTION CONTRIBUTE INDEPENDENTLY TO PROSTATE CANCER IMMUNE PRIVILEGE

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Background Despite the success of immunotherapy in immune-infiltrated "hot" tumors like melanoma, "cold" tumors like prostate cancer remain unresponsive [1,2,3]. We find that these tumors harbor regions of hypoxia that act as islands of immune privilege that exclude T cells, while retaining immunosuppressive myeloid cells. Targeting hypoxia using the hypoxia-activated prodrug, TH-302 (Evofosfamide) reduced hypoxic regions and co-operated with immune checkpoint blockade (anti-CTLA-4+anti PD-1) to drive tumor regression in transplantable and spontaneous murine prostate tumors [4]. In a Phase I clinical trial, the combination of Evofosfamide and anti CTLA-4 (Ipilimumab) elicited both objective responses and prolonged disease stabilization in late-stage "cold" tumor patients. However, Evofosfamide reduces but does not eliminate hypoxia and patient tumors resistant to treatment with Evofosfamide and Ipilimumab were hyper-metabolic [5]. Heightened tumor oxidative metabolism has been shown to generate hypoxic zones that resist PD-1 blockade therapy [6] and treatment with Metformin, a mitochondrial complex I inhibitor may reduce hypoxia and improve responses [7]. We hypothesized that targeting tumor oxidative metabolism using mitochondrial complex I inhibitors might diminish tumor hypoxia and, in conjunction with Evofosfamide, sensitize unresponsive tumors to immunotherapy.

Methods We investigated the capacity of two mitochondrial complex I inhibitors to reduce tumor oxidative metabolism, diminish myeloid suppressive capacity and improve anti-tumor T cell immunity, alone and in combination with Evofosfamide and checkpoint blockade. We assessed tumor burden and immune composition and characterized metabolic profiles using Seahorse XFe96 analyzer (Agilent).

Results While Evofosfamide or inhibition of oxidative metabolism alone did not significantly impact tumor regression, dual combination and triple combination with checkpoint blockade led to a significant reduction in tumor burden. Assessment of the tumor immune microenvironment identified improvements in CD8 and CD4 effector T cell proliferation. In vitro metabolic and functional profiling of TRAMP-C2 prostate tumors, pre-activated T cells and myeloid derived suppressor cells revealed differential effects of complex I inhibition, with inhibition resulting in reduced tumor proliferation and myeloid suppressive function but increases in proliferation and cytotoxic function of pre-activated T cells.

Conclusions Our findings indicate that tumor hypoxia and associated immune suppressive programming can be reduced through both local tissue remodeling and limitation of tumor oxygen metabolism. Complex I inhibition selectively inhibits tumor and myeloid cell function, while sparing T cells. This provides opportunities to craft synergistic immuno-metabolic therapies with the potential to treat "cold" tumor patients refractory to current FDA approved immunotherapeutics.

REFERENCES

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