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OXPHOS INHIBITION OFFSETS THE METABOLIC ADVANTAGE OF PANCREATIC CANCER AND PROMOTES A PRO-INFLAMMATORY TUMOR MICROENVIRONMENT

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Background Cancer cells must reprogram their metabolic state to adapt to the heightened energy demands needed for tumorigenesis.¹ Aberrant tumor metabolism rapidly exhausts the tumor microenvironment of oxygen and key nutrients, creating a hypoxic, immunosuppressive landscape that limits T cell infiltration and renders immunotherapy ineffective.² We have previously shown that targeted hypoxia reduction restores effector T cell infiltration and sensitizes tumors to anti-CTLA-4/anti-PD-1 blockade.³ Inhibitors of tumor oxidative metabolism (OxPhos) are also promising strategy to offset the tumor metabolic advantage over the immune system by reducing the oxygen utilization of tumor cells and combating tumor hypoxia. Metformin, a mitochondrial complex I inhibitor, has been reported to improve tumor control when combined with PD-1 blockade by alleviating tumor hypoxia and improving T cell activation.⁴ While targeting tumor oxidative metabolism has shown promising results, studies have mainly focused on the impacts of complex I inhibition, leaving the impact of inhibition on downstream components of the electron transport chain poorly understood.

Methods Napyradiomycin A1 (OxPhos complex I and II inhibitor), α TOS (OxPhos complex II inhibitor) and Atovaquone (OxPhos complex III inhibitor) were used to assess the differential impact of OXPHOS inhibition on mT4-2D PDAC tumor cells (derived from *Kras*^{+G12D}*TP53*^{+R172H}*Pdx1-Cre* (KPC) organoid cultures) (5) versus on T cells *in vitro* and *in vivo*.

Results We found that MT4-2D cancer cells treated with OxPhos complex II/III inhibitors *in vitro* showed no significant decrease in viability or proliferative capacity, however Atovaquone treatment decreased mitochondrial respiration potential based on reduced MitoRed staining in treated cells. We also found Ovalbumin-specific CD8⁺ T cells treated with Atovaquone during activation *in vitro* showed no significant reduction of T cell activation markers (CD44 and 4-1BB), as well as a minimal increase in T cell exhaustion marker expression (PD-1 and LAG3). Additionally, complex III inhibition during CD8⁺ T cell activation did not adversely impact IFN- γ production. OxPhos inhibitor treatment *in vivo* reduced the frequency of MDSCs within the tumor microenvironment and elicited increased CD8⁺ T cell infiltration.

Conclusions Here we show that inhibition of the complex II/III components of the mitochondrial OxPhos chain has the potential to offset the tumor metabolic advantage of the murine pancreatic cancer cell line MT4-2D. We found that these complex II/III inhibitors limit the metabolic fitness of MT4-2D while minimally compromising the activation state and function of cytotoxic T cells. Additionally, OxPhos inhibition repolarized the immunosuppressive tumor microenvironment, showing favorable potential for synergy with immune checkpoint blockade.

REFERENCES

1. Warburg O. On the origin of cancer cells. *Science*. 1956;123:3191: 309–314.
2. Liu A, Curren MA. Tumor hypermetabolism confers resistance to immunotherapy. *Seminars in cancer biology*. Academic Press. 2020;65.
3. Jayaprakash, et al. Targeted hypoxia reduction restores T cell infiltration and sensitizes prostate cancer to immunotherapy. *J Clin Invest* 2018;128(11):5137–5149.

4. Scharping Nicole E, et al. Efficacy of PD-1 blockade is potentiated by metformin-induced reduction of tumor hypoxia metformin improves PD-1 blockade immunotherapy. *Cancer immunology research* 2017;5.1:9–16.
5. Boj SF, Hwang C-I, Baker LA, et al. Organoid models of human and mouse ductal pancreatic cancer. *Cell* 2015;160:324–38. doi:10.1016/j.cell.2014.12.021

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