Targeting the androgen-indifferent state of prostate cancer through ferroptosis induction

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Background: Sensitivity to ferroptotic cell death has recently been shown to be an acquired vulnerability of therapy-resistant cancer cells across diverse lineages[1,2]. Previous data from a panel of patient-derived organoids have suggested that dependency on GPX4 to guard against ferroptotic cell death extends to the setting of AR-indifferent and neuroendocrine-like prostate cancer cells[1,2]. To explore the efficacy of ferroptosis induction for killing androgen-indifferent prostate cancer cells, we have begun to curate isogenic models of androgen-indifferent prostate cancer from collaborating labs and assess their sensitivity to GPX4 inhibition. Our results thus far confirm that androgen-indifferent prostate cancer cells are selectively vulnerable to ferroptosis induced by GPX4 inhibition and that this therapeutic hypothesis warrants further investigation.

Methods: A panel of LNCaP derivatives that model castrate-resistant prostate cancer (16D) and androgen-indifferent prostate cancer (42D and 42F) were procured from the Zoubeidi Lab[3]. 22Rv1 control and N-Myc overexpressing androgen-indifferent derivatives were procured from the Rickman Lab[4]. Small-molecule sensitivity profiling was performed as previously described[1].

Results: Both the LNCaP series of cells and 22Rv1 model demonstrate increased ferroptosis sensitivity of prostate cancer cells in the androgen-indifferent state. In the case of the LNCaP cells, relative sensitivity across the two androgen-indifferent cell lines (42D and 42F) correlates positively with previously characterized neuroendocrine-like features. Scaled area-under-the-curve values (smaller values correspond to increased sensitivity) for a canonical GPX4 inhibitor are as follow:

LNCaP cells	AUC	22Rv1 cells	AUC
16D	0.62	22Rv1	0.61
42D	0.30	22Rv1-N-Myc	0.31
42F	0.44		

Conclusions: Our results suggest that loss of androgen dependence in prostate cancer cells is accompanied by metabolic rewiring culminating in increased flux through pathways promoting the synthesis, mobilization and oxidation of phosphatidylcholine-derived polyunsaturated fatty acids.

References:

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Conflict of Interest: The authors declare no competing interests.

Acknowledgements: We gratefully thank Prostate Cancer Foundation for a Young Investigator Award to Vasanthi Viswanathan and the laboratories of Amina Zoubeidi (UBC), Leigh Ellis (DFCI) and David Rickman (Cornell) for sharing reagents and insights.