A therapy-resistant state of cancer cells relevant to neuroendocrine prostate cancer is susceptible to ferroptotic cell death

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Background
Cell state plasticity has been proposed to drive resistance to multiple classes of cancer therapies, thereby limiting their effectiveness. In the setting of prostate cancer, neuroendocrine transdifferentiation has been shown to yield AR-independent, therapy-resistant cells that survive standard-of-care therapy and give rise to lethal metastatic disease. However, an understanding of the mechanistic underpinnings of this state and its targetable vulnerabilities has remained incomplete. Here we molecularly characterize a therapy-resistant state of cancer cells that is relevant to AR-independent, neuroendocrine-like prostate cancer cells, and uncover its unique susceptibility to a non-apoptotic form of cell death known as ferroptosis.

Viswanathan, V. S. *et al.* Dependency of a therapy-resistant state of cancer cells on a lipid peroxidase pathway. *Nature* **547,** 453–457 (2017).
Hangauer, M. J., Viswanathan, V.S. *et al.* Drug-tolerant persister cancer cells are vulnerable to GPX4 inhibition. *Nature* **in press** (2017)**.**

Methods
Gene-expression signatures associated with therapy-resistance in patients were correlated with sensitivity of 516 cancer cell lines to 481 performance-diverse small molecules (Cancer Therapeutics Response Portal at portals.broadinstitute.org/ctrp). Results from this analysis were validated functionally using patient-derived organoid systems and inducible models of therapy-resistance models.

Results
Susceptibility to ferroptosis is a unifying theme extending across diverse therapy-resistant state contexts ranging from treatment-induced neuroendocrine transdifferentiation in prostate cancer, ZEB1-regulated EMT in epithelial-derived carcinomas to TGF-β-mediated therapy-resistance in melanoma. We show that this cell state is characterized by activity of enzymes that promote the synthesis of polyunsaturated lipids that are the substrates for lipid peroxidation via the action of lipoxygenase enzymes. This lipid metabolism creates a dependency on pathways converging on the phospholipid glutathione peroxidase (GPX4), a selenocysteine-containing enzyme that dissipates lipid peroxides and thus prevents the iron-mediated reactions of peroxides that induce ferroptotic cell death.

Conclusions
Our results suggest that apoptosis-resistant cancer cells, including AR-independent, neuroendocrine-state prostate cancer cells, have an enhanced ability to undergo ferroptosis, a non-apoptotic form of cell death. This finding points to a therapeutic strategy that combines ferroptosis induction with standard-of-care therapy to treat advanced prostate cancer as well as preventing the emergence of treatment-refractory disease by achieving more complete cell death response in the primary treatment setting.

Conflict of Interest

None

Funding Acknowledgements
NCI CTD2 U01CA176152, U01CA168397, NIH R01GM038627, HHMI