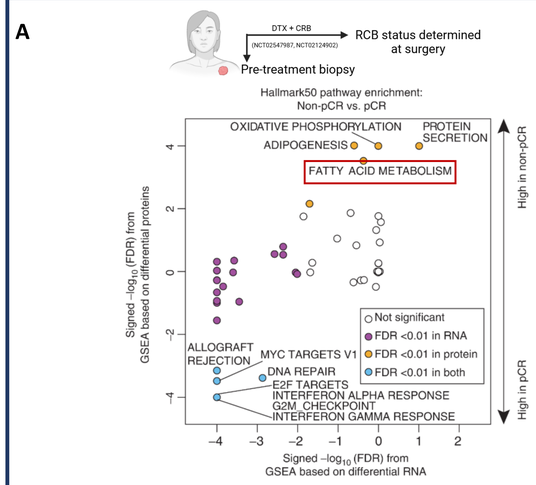
Acetyl-CoA fuels lipid storage to support triple negative breast cancer chemoresistance via ATP Citrate Lyase

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Introduction

- Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer where chemotherapy is the backbone of care.
- Oxidative phosphorylation (oxphos) is increased and a therapeutic vulnerability in chemoresistant TNBC (PMID: 30996079).
- The glucose oxidation pathway partially drives increased oxphos, but whether lipids could also contribute is unclear (PMID: 36813854).

Fatty acid metabolism is upregulated in residual TNBC



(Anurag, et al. Cancer Discovery, 2022)

A) Top upregulated protein pathways in patients who had residual cancer burden compared to pathological complete response.

Glucose oxidation may fuel increase in citrate and acetyl-coa in residual TNBC

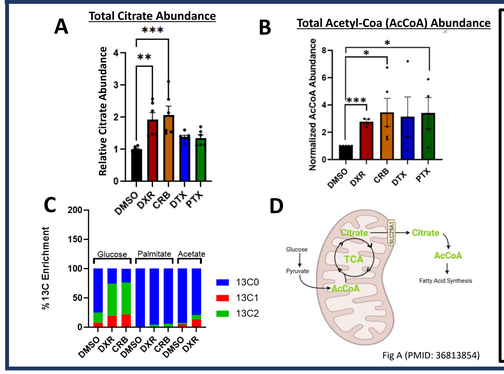
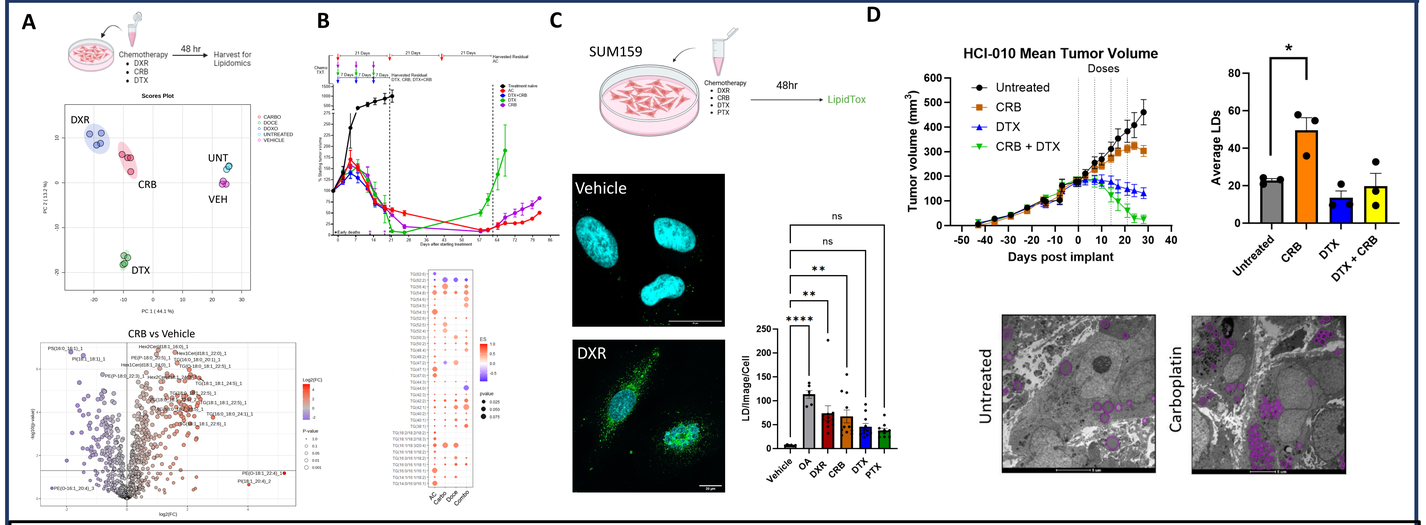


Fig A (PMID: 36813854)

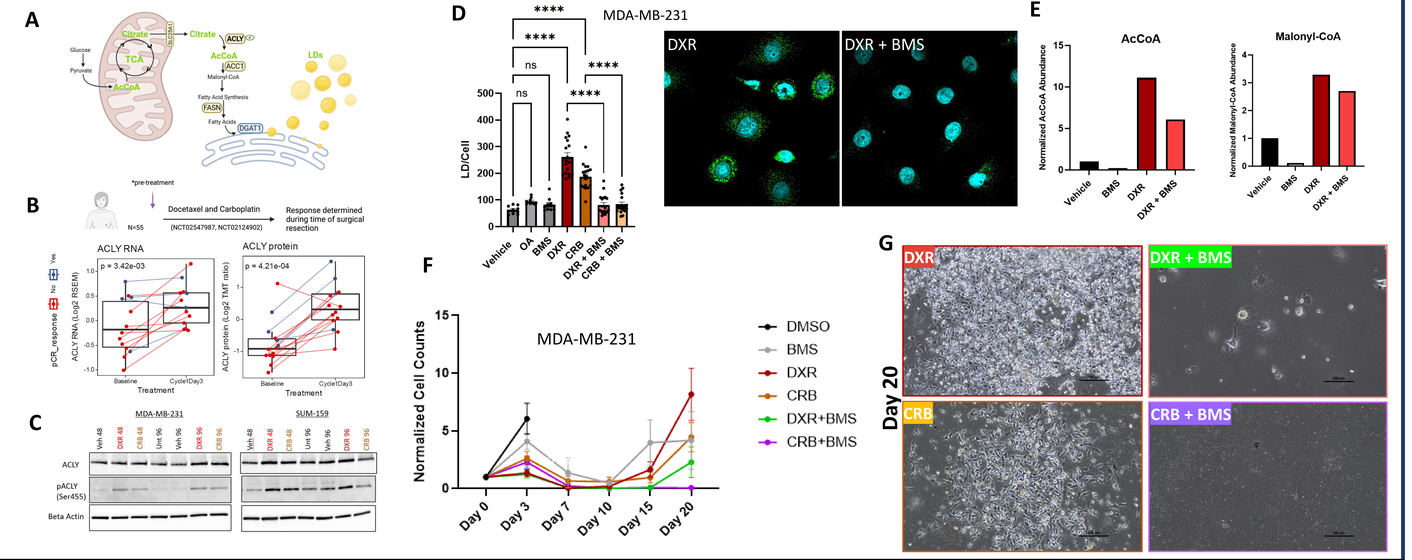
A) Citrate total abundance measurements in SUM159 cells after chemo. B) AcCoA measurements in SUM159 cells after chemo. C) Tracing of 13C-Glucose, Acetate, or Palmitate into AcCoA in DXR and CRB treated SUM159 cells. D) Diagram depicting glucose driven oxidation, leading to citrate export and AcCoA accumulation in the cytoplasm.

Lipid droplet accumulation in residual TNBC cells may support persister state and prevent lipotoxicity



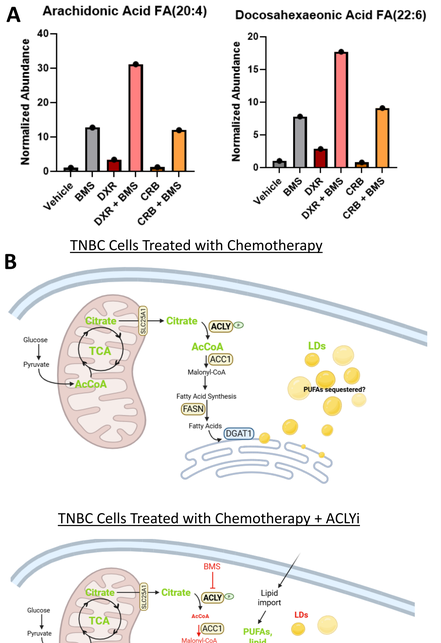
A) PCA diagram of lipid profiles of SUM159 cells treated with chemotherapy and a volcano plot depicting the top differentially expressed lipid species in carboplatin vs vehicle cells. B) Tumor growth plot of PIM001P treated with AC, CRB, DTX, or CRB+DTX, plus lipidomic assessment of the residual tumors vs the untreated tumor. C) Lipidtox experiments in SUM159 cells treated with chemotherapy. Representative images of the vehicle and doxorubicin cells are depicted, as well as a quantification of LDs/Cell. D) Tumor plot of the PDX HCI-010 treated with CRB, DTX, or the combination. TEM images from each tumor was analyzed for accumulation of LDs.

Ablation of ACLY reduces AcCoA, LD accumulation, and enhances chemosensitivity in residual TNBC cells



A) Diagram of fatty acid synthesis and LD accumulation driven by glucose oxidation and ACLY. B) Data from the CPTAC clinical trial depicting RNA, protein, and phosphorylation levels of ACLY in matched pre-treatment and on treatment biopsies (cycle1d3). C) Western blots of MDA-MB-231 and SUM159 cells treated with chemotherapy depicting protein expression levels of ACLY and pACLY at Ser455. D) Lipidtox experiment in residual MDA-MB-231 cells treated with chemotherapy and BMS. LDs/cell were quantified. Representative images of the DXR and DXR + BMS group are depicted. E) Abundance of AcCoA and Malonyl-CoA in MDA-MB-231 cells treated with DXR and DXR+BMS. G) Long term regrowth assay of MDA-MB-231 cells treated with chemotherapy and multiple doses of BMS. Representative images of the cells at the final regrowth day are depicted for chemotherapy alone or in combination with BMS.

ACLY ablation may promote lipid uptake and ferroptosis



A.) Total abundance of two PUFA lipid species after treatment with chemotherapy and BMS. B) Diagrams depicting the mechanism of cell death in TNBC cells treated with chemotherapy and BMS.

Summary and Future Directions

- Oxphos, AcCoA, FAS, and LDs are increased in TNBC cells surviving chemotherapy.
- Inhibiting ACLY can reduce AcCoA, LD accumulation, and sensitize the cells to NACT
- Future experiments will determine if lipid uptake induced by ACLY ablation causes increased PUFA accumulation and ferroptosis

Acknowledgements

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Diagrams made in BioRender.com