Background

About 30% of patients with hormone receptor positive (HR+) breast cancer will experience recurrence with therapy resistant disease. HR+ breast cancer typically expresses both estrogen receptor (ER) and progesterone receptor (PR) and is treated with endocrine therapies (ET) to block ER driven growth. Recurrent tumors consistently lose HR positivity and become resistant to these therapies leaving patients with limited therapeutic options. In order to target these populations, we developed a cohort of HR+ breast cancer cell lines with resistance to estrogen withdrawal (EWD; mimicking aromatase inhibition), Tamoxifen (TamR), and Fulvestrant (ICIR). Genetic analyses and lipid droplet staining on parental, EWD, and TamR T47D cells revealed a decrease lipid storage. While HR+ breast cancers exhibit active de novo fatty acid synthesis and visible lipid storage vehicles, this phenotype was lost or reduced in T47D-EWD and T47D-TamR cells.

We hypothesize that ET resistant breast cancers recycle rather than store lipids for metabolic use and membrane production/remodeling.

The following data presents additional models ET resistance to test this hypothesis. By elucidating the role of these changes in lipid biology with ET resistance, we aim to reveal therapeutic targets to improve standard therapies and prevent recurrence for HR+ breast cancer patients.

Objective & Methods

How does endocrine therapy resistance impact breast cancer lipid biology?

1. Evaluate effect of endocrine resistance on lipid storage formation. • Lipid droplet staining with Oil Red O and hematoxylin, light microscopy at 40X objective.
2. Use RNA-seq to identify lipid metabolic transcriptional changes in ET resistant cells compared to parental. • RNA-sequencing through UCD Genomics Core.
3. Define lipid profile of cells under different forms of ET resistance. • Metabolomics, LC-MS/MS, Metabolon, Agilent’s MassHunter software.
4. Analysis of metabolic phenotypic changes from ET resistance. • Seahorse XF Mito Stress Test, Agilent Palmitate-BSA FAO substrate, SeahorseXFe春风

Fig. 1: ET resistant cell lines alter lipid storage from sensitive parental cells.

Fig. 2: UCD4 cells display enriched lipid-related gene expression with ET resistance.

Fig. 3: ET resistance shifts global cellular lipidome of HR+ breast cancer cell lines.

Fig. 4: ET resistance differentially shifts mitochondrial metabolism in HR+ breast cancer cell lines.

Conclusions & Future Directions

Conclusions

• In both cell lines, TamR cells lose lipid storage phenotype while ICIR cells retain lipid storage. • All ET resistance cell lines display dysregulated lipid metabolic gene transcript expression by pathway analysis and significantly alter lipidome from parental cells.

• ET resistance does not impact FAO consistently across T47D and UCD4 cell lines.

Future Directions

• Assess fatty acid uptake vs. bioinversion in our resistance models. • Examine phenotype of resistance models in 3D growth conditions.

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