Modeling Breast Cancer in Men

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Background:
In 2023, 2,800 men are expected to be diagnosed with breast cancer in the United States, and while it affects a smaller patient population, breast cancer in men has a 19% higher mortality rate. Even though 87% of male breast cancers are estrogen receptor positive (ER+), breast cancer in men is resistant to anti-estrogen therapies. In this study we set out to characterize the difference between male and female breast epithelial cells to elucidate potential treatment pathways.

Project Methods:
We compared male and female epithelial cell lines from ultrasound guided breast biopsies of healthy men and women from the Susan G. Komen Tissue Bank that were processed using a culturing method developed in the lab. RNA-Seq of breast epithelial cells was done to identify unique signaling networks and genes in men, and RT-qPCR was used to determine the expression of ER signaling associated genes including ESR1, TBX3, FOXA1, GATA3 and APOBEC3B. Immunofluorescence for ERα was done to characterize differential expression and localization between men and women.

Result:
RNA-Seq identified an upregulation of ESR1 which correlates with increased ER+ male breast cancer, along with upregulation of non-genomic ER signaling pathway, including SRC activation, which may affect treatment response. Male cells also showed high levels KDM5D which is implicated in immune system evasion in esophageal cancer and colon adenocarcinoma. RT-qPCR displayed a two-fold increase in ESR1 and increases in TBX3 and APOBEC3B. Immunofluorescence identified ERα and localization to the cell membrane in men.

Conclusion:
This first characterization and modeling of men's breast epithelial cells provides the basis for determining the mechanism behind the lack of efficacy of anti-estrogen therapeutics. With further investigation of the increased non-genomic ER signaling in men, specifically the SRC pathway, we hope this will provide a pathway to treat male breast cancer through potential combination therapies.