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PS2-12-15 DO NOT TAKE PICTURES

Glucocorticoid receptor activation leads to remodeling of the chromatin landscape in infiltrating lobular carcinoma cells and changes in estrogen receptor-mediated gene expression

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Abstract

Background: Estrogen receptor positive (ER+) invasive lobular carcinoma (ILC) comprises 15% of all breast cancer and relies, in part, on ER signaling for cell proliferation and tumor growth. About 50% of ILC expresses glucocorticoid receptor (GR) which has been shown in infiltrating ductal carcinoma (IDC) to modulate ER-mediated gene expression[1,2] These previous studies showed that ligand-dependent GR occupancy inhibits ER occupancy at a subset of shared enhancer regions resulting in GR-mediated inhibition of ER-mediated proliferative gene expression.

Experimental Approach and Results: RNA-seq analysis of ER+ ILC cells treated with estradiol (E2), dexamethasone (Dex), or the combination (E2+Dex) revealed significant downregulation of cell cycle genes and upregulation of oxidative phosphorylation, mitochondrial function, and epithelial organization gene expression pathways. Using ChIP-qPCR, we found that ligand-bound GR is recruited to the same ER occupied *CCND1* enhancer element, resulting in loss of ER on chromatin and reduction in *CCND1* gene expression.

Conclusions: These results suggest that GR inhibits ER-mediated cell cycle progression through direct chromatin interaction at traditional ER-chromatin regulatory elements. *We hypothesize that ILC GR expression and activity can reprogram ER-mediated transcription.* The resulting reprogramming of estradiol-mediated gene expression in ILC may alter ILC biology and is the subject of ongoing experiments.

Background

GR expression occurs in ~50% of ER+ infiltrating lobular carcinomas

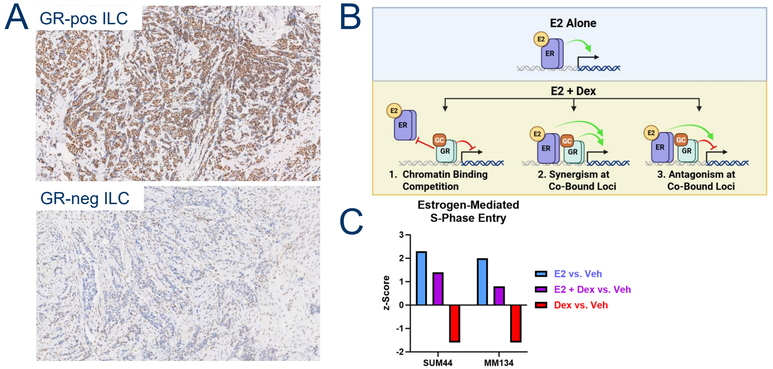


Figure 1. A) anti-GR IHC of primary ILC (n=25, 12 GR+, 13 GR-). B) Schematic of proposed GR interaction with ER transcription on chromatin. C) E2-mediated S-phase entry Ingenuity Pathway Analysis (IPA) gene expression pathway is induced with estradiol and relatively inhibited with GR activation (z-Score activation or repression is shown)[3].

Methods

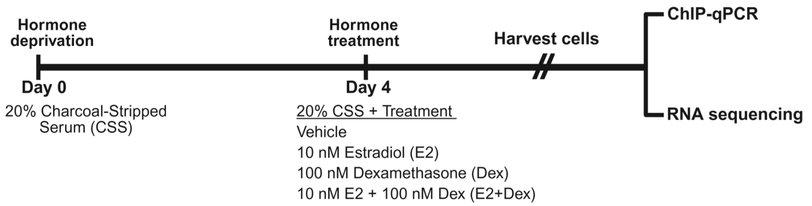


Figure 2. Experimental schema for RNA-seq and ChIP-qPCR in ER+/GR+ ILC cells

Results/Gene Expression

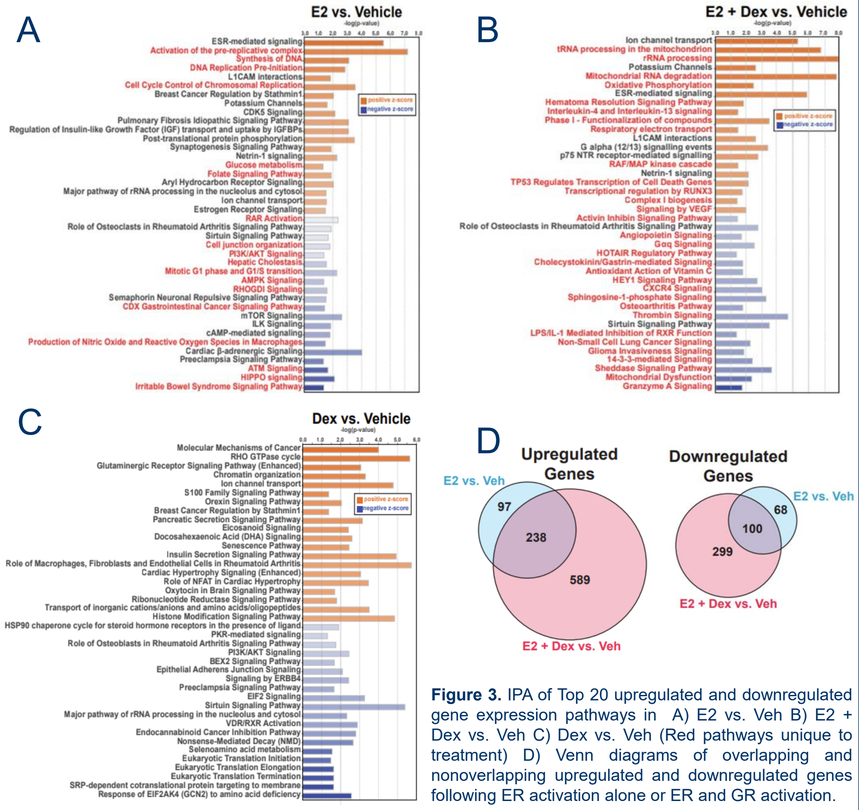


Figure 3. IPA of Top 20 upregulated and downregulated gene expression pathways in A) E2 vs. Veh B) E2 + Dex vs. Veh C) Dex vs. Veh (Red pathways unique to treatment) D) Venn diagrams of overlapping and nonoverlapping upregulated and downregulated genes following ER activation alone or ER and GR activation.

Results/anti-GR,ER Chromatin Immunoprecipitation

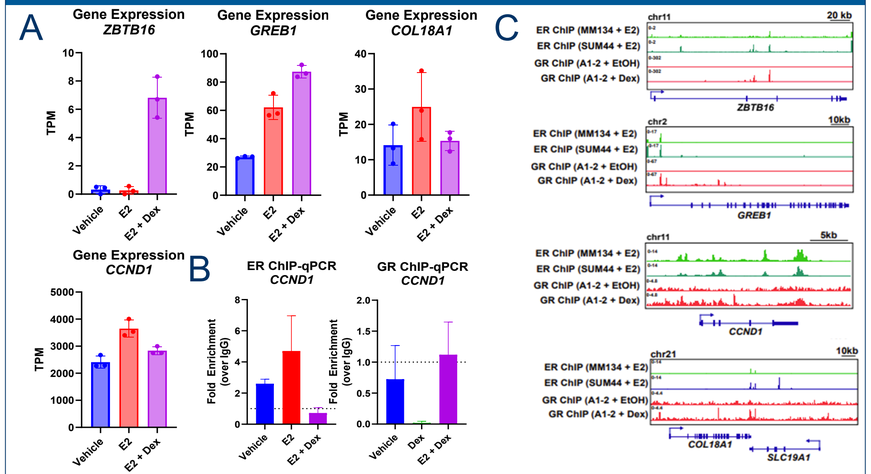


Figure 4. A) *ZBTB16*, *GREB1*, *COL18A1*, and *CCND1* relative gene expression with 10nM E2 and 100nM Dex in MM134 shows a variable effect on ER-mediated gene expression with concomitant GR activation. B) anti-ER ChIP-qPCR shows ER enrichment with E2 and loss of enrichment with E2+Dex, conversely anti-GR ChIP-qPCR shows enrichment with E2+Dex compared to Dex alone. C) Chromatin tracks of ER and GR under different conditions.[4,5]

Conclusions

- 50% of ILC expresses high levels of GR with most ILCs expressing ER.
- GR expression and activity in ILC and IDC has been associated with decreased cell proliferation. These data show that ER-mediated *CCND1* gene expression can be inhibited by ER displacement on chromatin following GR activation.
- Gene expression pathways suggest that GR and ER co-activation mediate different pathways compared to ER alone or GR alone.
- These data suggest that tumors that are ER+/GR+ compared to tumors that are ER+/GR- may have different biology.
- Ongoing studies integrating GR and ER chromatin binding with gene expression data will uncover the hormone-responsive chromatin landscape that contributes to functional crosstalk between GR and ER.

Acknowledgements

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REFERENCES: [1]West et al., 2016. [2]Tonsing-Carter et al., 2019. [3]Porter et al., 2023. [4]Nardone et al., 2022. [5]Archer et al., 1994.

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