Glucocorticoid Receptor is distinct from Androgen Receptor function in Castrate-Resistant Prostate Cancer

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Background

Prostate cancer is the most common cancer among men in the United States.

Diagnosis and treatment:

- PC is diagnosed by needle biopsy.
- Laparoscopic prostatectomies are treatments for localized PC.
- For metastatic PC, Androgen-Deprivation Therapy (ADT) is used to inhibit AR pathways. Prostate cancer cells develop resistance to ADT and become Castrate-Resistant Prostate Cancer (CRPC). In these cases, Enzalutamide has been a standard of care. However, Enzalutamide is ineffective in some patients, and resistance to Enzalutamide develops rapidly often leading to death.
- Novel treatments for CRPC are critically needed.

In a subgroup of CRPC patients, glucocorticoid receptor (GR) is highly expressed and active. GR can drive the growth of CRPC when AR is blocked, mimicking AR activity.

Therapies directed against GR-driven growth may be successful in treating CRPC.

Glucocorticoid receptor (GR) activity can recapitulate androgen receptor (AR) function in CRPC

Background Figure 2. GR is able to recapitulate AR function in AR-blocked prostate cancer.

- Androgen activates AR
- Enzalutamide blocks AR activity
- The addition of Dexamethasone activates GR allowing recapitulation of AR signaling

Hypothesis

It is unknown if GR has unique activities in CRPC other than recapitulating AR activity. We hypothesized that GR-driven CRPC has different activities than AR that promote progression to metastatic disease.

Background figure 3. Hypothesis: GR carries out additional functions compared to AR to drive CRPC progression.

Results

GR expression is higher in CRPC versus primary PC

Figure 1. GR(NR3C1) mRNA expression from patient sample cohorts. (unpublished Long et al.)

Many genes induced by Androgen and Glucocorticoid do not overlap

Figure 2. CRPC cells (CWR-22Rv1) were treated with Androgen (R), +/- Enzalutamide (E), +/- Dexamethasone (D) for 72 hours. RNA was collected from cells and total mRNA was sequenced. Differential genes expression was determined for Vehicle vs R and RED vs RE. (unpublished Long et al)

Figure 3. Ingenuity pathway analysis (IPA) was performed using the gene expression data from Figure2 (RED vs RE-R vsV). (unpublished Long et al)

GR activation regulates expression of Phosphodiesterases

Figure 4. This figure depicts the level of PDE2A, PDE11A, and PDE4B mRNA expression in 22Rv1 cells compared to the level of Beta-Actin mRNA expression. * p<0.05

Activation of GR induces the expression of pro-survival gene SGK1

Figure 5. Gene expression levels of SGK1 versus B-actin were measured by qRT-PCR using RNA from CWR-22Rv1 cells.

GR activation regulates the expression of neuroendocrine markers

Figure 6. Gene expression levels of CHGA and NSE versus B-actin were measured by qRT-PCR using RNA from CWR-22Rv1 cells. * p<0.05

Results

Cell Growth following treatment

Figure 7. The bar graph represents CWR-22Rv1 cell counts after 3 days of treatment. The series of images represent the cells after 3 day of treatment.

Findings

- GR is highly expressed in CRPC compared to primary PC
- The majority of GR-regulated genes do not overlap with AR-regulated genes
- Gene expression pathways including cAMP signaling pathway are regulated by GR but not by AR
- The expression of phosphodiesterases, which play a role in cAMP signaling, are regulated by GR
- SGK1, a pro-survival gene, is dramatically upregulated by GR with or without the presence of AR-signaling
- Neuroendocrine marker are GR-regulated

Summary

- Glucocorticoid receptor (GR) expression is increased in castrate-resistant prostate cancer compared to primary prostate cancer, thus indicating that GR activity increases after androgen deprivation.
- GR-activation in androgen receptor (AR)-blocked cells induces different genes than AR, suggesting that GR-driven CRPC is unique from AR-driven disease.
- The discovery of novel mechanisms by which GR drives PC progression may reveal therapeutic targets for advanced PC

References

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