A novel Glucocorticoid Receptor (GR) antagonist overcomes GR-mediated chemoresistance in Triple Negative Breast Cancer

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ABSTRACT

The Glucocorticoid Receptor (GR) is a member of the nuclear receptor superfamily of ligand-activated transcription factors that is activated by steroid hormones including glucocorticoids, and by synthetic glucocorticoid drugs such as dexamethasone. Several preclinical studies have shown that GR mediates resistance to both targeted therapies and conventional chemotherapies in epithelial cancers, such as prostate, bladder, renal, ovarian and triple negative breast cancers (TNBC) (Gassler et al. 2005, Li et al. 2017, Zhang et al. 2007). In TNBC, both GR activation and a disrupted cell cycle are associated with poor prognosis, chemotherapy resistance, and increased recurrence (Pan et al. 2011, Skor et al. 2013). Therefore a molecule that inhibits GR activation could attenuate the development of resistance to chemotherapy, the standard of care for patients with advanced TNBC. We are developing novel GR inhibitors that effectively block GR transcriptional activity in cells competing for ligand binding and blocking GR-Coactivator interactions. In vitro, GR inhibition by OP-3713 blocks transcription of GR-mediated target genes and enhances the efficacy of chemotherapeutic agents in TNBC cells under GR activation by dexamethasone. In humans, the predominant glucocorticoid is cortisol, while in mice the predominant glucocorticoid is corticosterone (Sawamoto et al. 2008), which is a potent agonist of murine GR but a weak agonist of human GR. Therefore it is necessary to provide exogenous cortisol to fully activate GR. Using xenograft models of triple negative breast cancer, we find that tumors grown in mice with physiologically relevant circulating cortisol levels are significantly less sensitive to standard of care chemotherapy than those grown in the absence of cortisol. Inhibition of GR by OP-3713 prevents tumor relapse following chemotherapy treatment. We have begun to elucidate the mechanisms by which GR mediates chemoresistance in TNBC and its reversal by OP-3713. Our findings indicate the important role of GR as a mediator of resistance in TNBC and demonstrate the therapeutic potential of GR inhibitors in combination with clinically utilized chemotherapeutics.

RESULTS

OP-3713 blocks GR transcriptional activity and restores apoptosis induced by chemotherapy in TNBC cells in vitro

The synthetic glucocorticoid dexamethasone (Des) robustly activates endogenous GR target gene expression, such as FKBP5, in MDA-MB-231 and HCC1806 TNBC cells. OP-3713 blocks FKBP5 gene induction in a dose-dependent manner.

GR Activation Protects Against Chemotherapy in TNBC Cancer Cells

MDA-MB-231

HCC1806

Vehicle

OP-3713

DMSO

Dex 30nM

OP-3713

3 weeks

15 min

6 h

Schematic of a PKPD study to measure the effect of OP-3713 on Dexamethasone-induced target gene expression in HCC1806 xenografts. Dexamethasone at 0.5mg/kg/animal robustly activates endogenous expression levels of two established GR target genes, FKBP5 and GILZ, in HCC1806 xenografts in vivo and OP-3713 blocks this GR transcriptional activity in a dose-dependent manner.

GR is Active in Tumors Grown in Mice on Cortisone Water

MDA-MB-231 and HCC1806 cells were treated with 100 nM paclitaxel in the presence or absence of 30 nM Dexamethasone (Des) and 500 mg/M paclitaxel. Dexamethasone treatment protected cells from chemotherapy-induced apoptosis, and this effect is reversed by OP-3713.

CONCLUSIONS

- GR inhibition by OP-3713 blocks transcription of GR-mediated target genes under GR activation by dexamethasone both in vitro and in vivo.
- GR activation by physiological levels of ligand protects tumor cells against chemotherapy in vitro and this effect is reversed by OP-3713.
- GR activation in MDA-MB-231 significantly enhances invasion and metastasis.
- GR inhibition by OP-3713 prevents the relapse of TNBC tumors after chemotherapy.