Glucocorticoids Promote Granulosa Cell Tumor Growth and Antagonize Paclitaxel Via a FOXL2 c.C402G-dependent Mechanism

Robert T. Hillman, MD, PhD – UT MD Anderson Cancer Center

Topic: Ovarian

Objectives
Nearly all adult-type granulosa cell tumors of the ovary (aGCTs) carry the same oncogenic mutation in the Forkhead family transcription factor FOXL2 (c.C402G; p.C134W). A key unmet need in the treatment of this disease is the development of targeted therapies that exploit the high prevalence of FOXL2 c.C402G mutations. The objective of this study was to leverage novel genetic aGCT models and high-throughput drug screening to identify therapeutic vulnerabilities specific to the presence of the pathognomonic FOXL2 c.C402G mutation.

Methods
CRISPR/Cas9 was used to generate isogenic derivatives of KGN, a cell line derived from a recurrent aGCT. Parental cells (KGN-FOXL2WT/C402G) or isogenic cells lacking both FOXL2 alleles (KGN-FOXL2—/—) were functionally characterized and loss of Foxl2 protein was confirmed by immunoblot. A high-throughput, image-based assay was used to screen a total of 2,416 compounds (including all FDA-approved drugs) across a range of concentrations for growth inhibition in KGN-FOXL2WT/C402G cells and KGN-FOXL2—/— cells. Hafner growth rate inhibition models were used to identify compounds with pharmaco-genetic selectivity for inhibition of aGCT cells expressing FOXL2 c.C402G. A Bliss independence model was used to assess the synergy/antagonism of drug combinations. Validation experiments were conducted using a diverse biobank of patient-derived organoids.

Results
In the primary drug screen, glucocorticoids as a class were found to stimulate proliferation of KGN-FOXL2WT/C402G cells with nanomolar EC50, whereas they lacked this activity in KGN-FOXL2—/— cells (Fig. 1A). Notably, three glucocorticoid pro-drugs (cortisone, prednisone, cortisone acetate) lacking in vitro activity were included in the screen and did not show growth promoting activity, as expected (Fig. 1A arrowheads). A pure mineralocorticoid, deoxycorticosterone acetate, did not promote aGCT growth, indicating a high specificity for glucocorticoid activity (Fig. 1B). Patient-derived tumor organoids recapitulated the immunophenotype of the original tumor (Fig. 1C) and the growth promoting effect of glucocorticoids was observed in some aGCT organoids (Fig. 1D). Sensitivity to glucocorticoid stimulation could be partially rescued by restoring Foxl2 to KGN-FOXL2—/— cells. Glucocorticoids are frequently administered to reduce nausea and infusion reactions associated with paclitaxel, a chemotherapy agent frequently used in the treatment of aGCT. Formal drug combination testing demonstrated a difference from Bliss model indicating significant antagonism between dexamethasone, a high potency glucocorticoid, and paclitaxel.

Conclusions
Glucocorticoids promote aGCT growth in a FOXL2 c.C402G-dependent manner. Co-administration of dexamethasone antagonizes the anti-tumor effect of paclitaxel in models of this disease. Modulation of glucocorticoid signaling is a promising pharmaco-genetic therapeutic target in aGCT.

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