Abstracts

EP003/#1114 IDENTIFICATION OF MOLECULAR TARGETS AND PATHWAYS FOR IMPROVING ENDOMETRIAL CANCER RACIAL DISPARITIES

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Objectives Identify proteins present at significantly different levels in endometrial cancer specimens across 4 racial groups to direct future therapy.

Methods Proteins extracted from endometrioid endometrial cancer specimens of women who self-identified as Black, American Indian, or White (N=12 each), or Asian (N=10) were measured by Tandem Mass Tag liquid chromatography-tandem mass spectrometry. Patients were matched for age and body mass index. Significant differences in protein levels were identified by ANOVA after adjustment of the first principal component and evaluated by Ingenuity Pathway Analysis. Drug effects on human Ishikawa endometrial cancer cells were evaluated using an MTT assay.

Results The only patient characteristics significantly different across racial groups were higher rates of diabetes in Blacks and hypertension in Whites. Fifty-eight proteins exhibited significant differences across all groups. The most significant pathways identified to be regulated by proteins significantly different in non-Whites compared to Whites are regulators of protein synthesis. Trametinib and 2-deoxyglucose inhibition of mitogen-activated protein kinase 3 and hexokinase-2, which were significantly upregulated in specimens from Blacks compared to Whites, reduced growth of endometrial cancer cells with half-maximal inhibitory concentrations of 3 uM and 3 mM, respectively, but did not interact synergistically.

Conclusions This study demonstrated significantly different protein expression profiles in endometrioid endometrial cancers across 4 races. These proteins represent candidate biomarkers and drug targets for development of strategies to improve disparate outcomes of endometrial cancer patients.

EP004/#741 DNA METHYLATION LANDSCAPE AS A POTENTIAL PLAYER IN ACQUIRED-DRUG RESISTANCE IN OVARIAN CANCER

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Objectives Development of therapeutic resistance is a major cause of mortality in high-grade serous ovarian cancer (HGSOC), thus a better understanding of acquired resistance mechanisms is needed. This study aimed to investigate how epigenomic events might be associated with acquired-drug resistance in HGSOC patients.

Methods Methylation and gene expression differences between primary platinum-sensitive (n=32) and recurrent acquired-resistant samples (n=28) was explored using a HGSOC dataset. High resolution melting was used to validate results using epithelial ovarian cancer cell lines and HGSOC tumours. A CRISPR-Cas9 approach was used to investigate the effects of DNA methylation editing in vitro. Plasma samples from HGSOC patients (n=17) and age-matched healthy controls (n=20) were used to investigate longitudinal methylation dynamics via droplet digital PCR.

Results Comparison of methylation and gene expression analysis identified several genes, known to be involved in diverse immune and chemoresistance-related pathways, that significantly differentiated between paired platinum-sensitive and acquired-resistant HGSOC samples, with three genes displaying the most consistent methylation changes (PDCD1, NKAPL, APOBEC3A). A CRISPR-Cas9 approach was used to interrogate the effects of APOBEC3A and NKAPL promoter methylation editing on platinum sensitivity, with demethylation of NKAPL promoter being associated with increased platinum sensitivity. Hypermethylation of NKAPL and APOBEC3A were detected in 46% and 69%, respectively, of plasma samples from women with relapsed HGSOC.

Conclusions Promoter methylation has been identified as potentially involved in HGSOC drug resistance. Further research is warranted to understand the future use of these methylation patterns as prognostic/predictive markers in the OC clinical setting.

EP005/#572 EXPLOITING SMARCA2 DEPENDENCY FOR TARGETED THERAPY IN SMARCA4-DEFICIENT OVARIAN CANCERS

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Objectives Most ovarian cancer (OC) patients recur after first-line treatment and develop chemoresistance, highlighting an unmet need for precision medicine in OC. Half of OCs harbor mSWI/SNF chromatin-remodeling complex alterations including 10% in the SMARCA4 gene. Studies to date have suggested that the catalytic subunits of the mSWI/SNF complex, SMARCA2 and SMARCA4, exhibit paralog dependency and thus present an opportunity for synthetically lethal molecular targeting. The aim of this study is to investigate SMARCA2-dependency in SMARCA4-deficient OCs and to identify synthetic lethal interactions of SMARCA2-protein degradation in these cancers.

Methods Using CRISPR-Cas9 lentiviral-transduction targeting the SMARCA4 gene, we developed novel murine syngeneic/isogenic OC cell lines from well-characterized cell lines Id8 and UPK10, and novel electropropagation-based genetically engineered mouse model-derived cell line 3_1. Human isogenic
OC cell lines OAW28 were also derived using the same technique. SMARCA2 protein degrader (proteolysis-targeting chimera) was provided in collaboration with industry. Western blots were performed to define paralog dependency in SMARCA4-deficient cells and to assess adequate SMARCA2-degradation. SMARCA2 protein degrader response was assessed using viability assays.

**Results** SMARCA4-deficient isogenic OC cell lines displays increased SMARCA2 protein expression compared to SMARCA4-wildtype cells, suggesting that paralog dependency exists in OC. Furthermore, near complete SMARCA2-degradation occurs at low nanomolar range after 6-hour incubation. Comparing IC_{50} values, we show a 5-fold increased sensitivity to the SMARCA2 protein degrader in SMARCA4-deficient OC cell lines compared to control, suggesting a synthetic lethal interaction in these cancers.

**Conclusions** This study identifies SMARCA2 protein degradation as a unique therapeutic vulnerability and potential therapeutic target for SMARCA4-deficient OCs.

**EP006/#812**

**THE EXPRESSION LEVEL OF OBESITY AND LIPID METABOLISM RELATED GENES CONDITIONS TUMOR BEHAVIOR AND SURVIVAL IN GYNECOLOGICAL CANCERS**

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**Objectives** Currently, the carcinogenesis of thirteen neoplasms has been related to obesity. Of the gynecological ones, endometrial and ovarian cancers are associated with it. To date, obesity is defined based on BMI (\(\geq 30 \text{ kg/m}^2\)). However, not all obesity is associated with a metabolic disorder (healthy-metabolic-obesity or HMO). Likewise, there are individuals with normal BMI (\(< 25 \text{ kg/m}^2\)) who are carriers of metabolic disorders. The objective of this study was to establish whether the abnormal expression of obesity- and lipid metabolism-related genes could determine the biological behavior and survival of the most prevalent gynecological cancers.

**Methods** To do this, we built a 2208 obesity/dyslipidemia/hypercholesterolemia-related gene dataset (ODH) according to phenopedia (PGHKB (v7.7)). We then downloaded TCGA endometrial (UCEC=543-cases), cervical (CESC=304-cases) and ovarian (OVCA=374-cases) cancers RNAseq datasets. NMF-consensus clustering, differential-gene-expression-analyses (DGEA), Gene-set-enrichment (GSEA) and Gene-Ontology (GO) analyses were carried out, and Kaplan-Meier survival curves were built up. Significantly up- or downregulated genes were defined as those with logFC\(\geq 1.5\) at non-adjusted p-values \(\leq 0.01\).

**Results** Based on ODH-gene expression, we identified UEC, CESC and OVCA clusters with significantly different overall survival (OS). Regarding UEC, a cluster allocates the high-copy-number endometrioid-variant as well as the serous type (worse prognosis), in a similar manner as observed with the mesenchymal-variant in high-grade-serous ovarian cancer (see figure 1). Interestingly, the GSEA and GO-analyses show that for worse prognosis histologies exhibit different enrichment patterns regarding antitumor immune response, TGF-beta (EMT)-mediated signaling, lipid metabolism and inflammatory response (all cancer hallmarks).

**Conclusions** These in-silico findings support the role of obesity in conditioning behavior/therapeutic response/prognosis of these gynecologic cancers. (Supported by fondecyt_1201083)