Identification of Molecular Targets and Pathways for Improving Endometrial Cancer Racial Disparities

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Objective: 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 are 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, NFKB, APOBEC3A). A CRISPR-Cas9 approach was used to interrogate the effects of APOBEC3A and NFKAP promoter methylation editing on platinum sensitivity, with demethylation of NFKAP promoter being associated with increased platinum sensitivity. Hypermethylation of NFKAP 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.

Exploiting SMARCA2 Dependency for Targeted Therapy in SMARCA4-Deficient Ovarian Cancers

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Objective: 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 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 electroporation-based genetically engineered mouse model-derived cell line 3_1. Human isogenic