EP111/#1490 PROTEOGENOMICS DELINEATE PATHOGENESIS, MOLECULAR CHARACTERISTICS, AND PREDICTORS OF PROGESTIN RESPONSE IN EARLY-ONSET ENDOMETRIOID ENDOMETRIAL CANCER

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Introduction Endometrial carcinoma (EC) remains a public health concern with a growing incidence particularly in younger women. Women with early-onset endometrioid EC (EEEC) who wish to maintain fertility are a worldwide concern, and biomarkers for predicting which patients will respond to progestin-based fertility-sparing therapy are a major unmet clinical need.

Methods To comprehensively characterize the proteogenomic characteristics of the early-onset endometroid endometrial carcinoma (EEEC), we conducted a multi-omics study (genomics, and proteomics) with FFPE tissues from paired tumor and normal tissues of 222 endometrioid ECs (including 81 EEECs younger than 40 who mainly received fertility-sparing treatment) and 14 atypical endometrial hyperplasia (AEH) patients from Tongji and Fudan Hospital (TJFD cohort) in China.

Results EEEC was featured by exclusive germline muataions,a higher BMI and downstream dysregualted lipid metabolism signaling. Our integrated multi-omics analysis unexpectedly revealed an exposome-related mutational signature to be associated with EEEC leading to EEEC specific CTNNB1 and SIGLEC10 hotspot mutations and downstream protein pathway disturbance. Interestingly, in EEECs SIGLEC10^{Q144K} mutation resulted in aberrant Siglec-10 protein expression and promoted progestin resistance by interacting with ERα. We identified and validated four (EEF1E1, ILVBL, SRPK1 and NUDT5) biomarkers of progestin resistance.

Conclusion/Implications Our study provides a unique high-quality proteogenomic resource of EEECs, and explicates the distinct clinical and molecular characteristics of EEECs, encompass-ing obesity, genetic susceptibility, and environmental exposure, that are concomitant with pathogenesis and progestin resistance. Furthermore, we identified biomarkers for progestin response in EEEC fertility-sparing treatment. These attributes can be utilized to promote primary prevention and early detection of EEECs

EP112/#1491 PROTEOGENOMICS DECIPHER DISTINCT METASTASIS PATTERNS AND BIOMARKERS OF ENDOMETRIAL CARCINOMA

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Introduction Endometrial carcinoma is a common gynecologic malignancy, and lymph node metastasis greatly affects patient outcomes. Proteogenomics analysis has emerged as a powerful tool for identifying molecular mechanisms involved in cancer progression and metastasis, offering potential for biomarkers discovery and personalized treatment strategies.

Methods In this study, we utilized WES, proteomics, and multiplex immunohistochemistry to investigate the metastasis patterns of different molecular subtypes in a cohort of 96 EC patients with lymph-node metastasis and 126 without metastasis. Our aim was to elucidate the molecular characteristics that distinguish between these two groups and identify potential biomarkers for metastasis.

Results Proteogenomics analysis identified two distinct metastasis patterns of EC associated with TME. One pattern is characterized by an immune-cold phenotype, which is predominantly observed in patients with the MSI subtype. These patients often exhibit JAK1 mutations, defects in immunoproteasome components and HLA complexes, leading to deficiencies in antigen presentation pathways, resulting in immune evasion. The other is characterized by an immune-hot phenotype, mainly distributed in the CNL and few MSI subtype, with significant infiltration of macrophages and upregulation of integrin pathways, promoting tumor cells to undergo mesenchymal transition. Additionally, we explored and validated three consensus biomarkers shared across diffrerent molecular subtypes for predicting lymph-node metastasis.

Conclusion/Implications Our research provides an unprecedented large-scale multi-omics resource of lymphatic metastasis EC, offering novel insights and new biomarkers for effectively stratifying high-risk patients for lymphatic metastasis. We have deciphered two distinct metastasis patterns in EC, which can be exploited for the development of personalized screening and targeting strategies.

EP113/#220 COMPOUND AC1Q3QWB UPREGULATES CDKN1A AND SOX17 VIA INTERRUPTING THE HOTAIR-EZH2 INTERACTION AND ENHANCES THE EFFICACY OF TAZEMETOSTAT IN ENDOMETRIAL CANCER

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Introduction Endometrial cancer (EC) is a common female reproductive system malignant tumor, with increasing incidence rates and poor prognosis in recurrent/metastatic cases. The interaction between long non-coding RNA HOTAIR and polycomb repressive complex 2 (PRC2) causes the abnormal suppression of tumor suppressors, which plays a crucial role in tumor development. This study aims to investigate the potential of AC1Q3QWB (AQB) to interrupt the HOTAIR-EZH2 interaction in EC and evaluate a novel combination therapy of AQB and tazemetostat (TAZ).

Methods RNA immunoprecipitation (RIP) and chromatin isolation by RNA purification (ChIRP) assays were utilized to verify the interference of AQB with HOTAIR-EZH2 interaction in EC cells. The Agilent Human ceRNA Microarray was employed to identify tumor suppressors upregulated by AQB and TAZ, while the chromatin immunoprecipitation (ChIP) assay was performed to investigate the mechanism of genes activation. The combination therapy of AQB and TMZ was used for in vivo experiments.

Results AQB inhibited HOTAIR and EZH2 binding in EC cells, restoring the expression of numerous tumor suppressors. In vitro, the combination of AQB and TAZ produced a