Conclusion PDOs demonstrated intra and inter-patient transcriptional heterogeneity, with variations in CSC, EMT and drug transporter related genes observed, mirroring the complexity of HGSC. Our data indicates that the potential use of PDOs as representative models for drug screening or development should incorporate multiple metastatic sites to accurately reflect the spatial heterogeneity of HGSC.

#1410

Single-Cell RNA Sequencing Analysis Highlights M2-Like Tumor-Associated Macrophages' Role In Poor Response To Radiotherapy In Cervical Cancer

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Introduction/Background Cervical cancer treatment with concurrent chemoradiotherapy (CCRT) is often limited by poor response in a subset of patients. M2-like tumor-associated macrophages (TAMs) are known to create an immune-suppressive microenvironment that promotes tumor progression and may drive treatment resistance. This study combines single-cell RNA sequencing (scRNA-seq) with in vitro validation to investigate the role of M2-like TAMs in poor response to CCRT.

Methodology scRNA-seq data from five CCRT-poor response and five CCRT-good response patients were analyzed. M2-like TAMs were compared between groups, focusing on differential gene expression and pathway enrichment. Integration methods addressed sample heterogeneity

Results Analysis identified 14 distinct cell types, with M2-like TAMs significantly enriched in poor-response samples. DEG analysis revealed upregulation of key genes in poor-response M2-like TAMs, including IFNL3 (log2FC = 9.2), DAPK1-IT1 (log2FC = 9.1), and CCL18, associated with immune suppression, cytokine signaling, and extracellular matrix reorganization.

GO enrichment analysis highlighted pathways such as leukocyte chemotaxis, driven by CCL18, which recruits immunosuppressive cells to the tumor microenvironment. Interferon signaling dysregulation and extracellular matrix organization pathways were also significantly enriched, indicating roles in immune evasion and tumor invasion. Additionally, metabolic shifts favoring glycolysis and lipid metabolism were observed, reflecting a tumor-supportive phenotype.

In vitro experiments confirmed the functional role of M2-like TAMs. Polarized M2-like macrophages significantly enhanced cancer cell survival following radiotherapy compared to M1-like macrophages ($p < 0.01$). Elevated CCL18 secretion correlated with reduced sensitivity to cisplatin, and neutralizing CCL18 partially restored sensitivity. Knockdown of IFNL3 in macrophages enhanced T-cell activation and tumor cell apoptosis, further validating its role in immune suppression.

Conclusion This study reveals that M2-like TAMs play a pivotal role in poor response to CCRT in cervical cancer patients. Targeting M2-like TAM-specific pathways offers a promising avenue for therapeutic intervention to enhance radiotherapy efficacy. Future studies will extend these findings to larger cohorts and explore the application of TAM-focused therapies.

Disclosures NO disclosure

#1418

Phosphatidylserine Decarboxylase Overexpression Induced Reprogramming Of Fatty Acid Metabolism Confers And Platinum Based Chemoresistance In P53 Dependent Manner In Epithelial Ovarian Cancer

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Introduction/Background Metabolic reprogramming, particularly the shift from glycolysis to oxidative phosphorylation, plays a critical role in cancer progression and response to therapies. Notably, phosphatidylserine decarboxylase (PISD), a mitochondria specific phospholipid enzyme that converts phosphatidylserine (PS) to phosphatidylethanolamine (PE), is though to be crucial from cancer dynamics and treatment resistance. However, its role in epithelial ovarian cancer (EOC) has not yet been elucidated. Therefore, this study aims to investigates its role in EOC identify as a new therapeutic target.

Methodology The mRNA level of PISD was determined using data from the Gene Expression profiling and RNA sequencing. Protein levels of PISD were evaluated through immunohistochemistry staining of EOC, borderline, benign, and normal epithelial tissues. The association between PISD expression and its association with clinicopathological features and prognosis were analyzed. Furthermore, functional studies more performed in ovarian cancer

Results RNA sequencing and public database analyses revealed elevated PISD mRNA and protein levels in EOC. High PISD protein level was also observed in EOC compared with those of borderline and benign tumors and nonadjacent normal epithelial tissue in association with serous cell type, advanced FIGO stage, high tumor grade and platinum resistance (all $P<0.001$). Also, poor overall survival and disease-free survival ($P<0.001$). Furthermore, functional studies demonstrated that PISD knockdown enhances cisplatin-induced apoptosis in OVCA429 and OVCA433 cells, mediated through increased reactive oxygen species (ROS) and activation of the p53 signaling pathway. Elevated p53 level correlated with heighted apoptosis, while inhibition of p53 diminished this effect, confirmed, confirmed a p53 dependent mechanism of increased chemosensitivity to cisplatin in EOC.

Conclusion Our study demonstrates that PISD overexpression is linked to platinum based chemoresistance in EOC, mediated through ROS and p53 pathways. Targeting PISD may thus offer a novel approach enhance chemosensitivity and improve clinical outcome.

Disclosures No disclosure

#1530

Characterization Of The Immuno-Oncological Transcriptomic Landscape Of Uterine Smooth Muscle Tumors Of Uncertain Malignancy Potential (STUMP) According To Clinical Outcome

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Introduction/Background Uterine smooth muscle tumors of uncertain malignancy potential (STUMP) present diagnostic and clinical challenges, ambiguous histopathological characteristics, and potential for recurrence, sometimes as leiomyosarcoma. Novel diagnostic and prognostic markers are needed to improve STUMP's management.

Methodology Eleven STUMP samples, diagnosed according to the 2020 WHO Classification of Female Genital Tumours, were collected, and a representative series of leiomyomas and leiomyosarcomas. Gene expression profiling was analyzed using the nCounter PanCancer IO 360 Panel (NanoString® Technologies), targeting 770 mRNAs related to tumor biology, immune microenvironment, and immune response.

Results The analyzed series included 11 STUMP cases (5 relapsed [rSTUMP] and 6 non-relapsed [nrSTUMP]), 11 leiomyosarcomas, and 11 leiomyomas. Comparison between all STUMP and LM did not reveal any differentially expressed genes. However, nrSTUMP cases showed