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Abstract 2491: The Oxford Classic can identify HGSOC patients who may benefit from EMT-targeting therapies FREE

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Abstract

Introduction: Despite development of novel targeted therapies such as PARP inhibitors and anti-angiogenic drugs, there is a clear lack of treatment options for High Grade Serous Ovarian Cancer (HGSOC) patients who are Homologous Recombination Repair proficient (50% of cases) and those with intrinsic resistance to these drugs. In this study we demonstrate the ability of the Oxford Classic (OxC)[1,2], a non-genetic classifier, to identify HGSOC patients who may benefit from EMT targeting drugs.

Methods: 139 HGSOC diagnostic tumor tissue (Brescia cohort) underwent RNA sequencing. Scottish cohort[3] was used for external validation and TCGA, AOCS & OVCAD datasets were used for meta-analysis. Deconvolution of tumor RNAseq data, survival analyses, differential gene expression (DGE) analysis, gene pathway analyses in R and tumor immune profiling using CIBERSORT were performed.

Results: Risk stratification of HGSOC using the Oxford Classic Patients with a higher OxC-EMT score had 3.6 times increased risk of death (95%CI: 1.6-8.0; p=2e-03) compared to patients with a lower OxC-EMT score by a multivariable cox regression analysis of Brescia cohort. By Kaplan-Meier survival analyses, a significant difference in overall survival in Brescia cohort (p=9e-06), Scottish cohort (p=2e-03) and a combined set of 1023 cases (p=1e-04), was observed between EMT-low risk patients (OxC-EMT score-0) and EMT-high risk patients (OxC-EMT score>0). Notably, 5-year median survival of EMT-low risk and EMT-high risk group was 50% and 13%, resp. (95%CI: 36.1%-69.3% vs 7.1%-23.5%) in Brescia cohort. Therapeutic options for OxC-EMT-high risk group DGE analysis of EMT-low patients and EMT-very high patients (OxC-EMT score>0.5) identified 404 differentially expressed genes common to the datasets. These included genes related to extracellular matrix organisation (VCAN, TGFβI), epithelial cell proliferation (RUNX2, FABP4, SERPINF1), cell chemotaxis (CCL19, DUSP1), angiogenic factors (VEGFC, CXCL12) and transmembrane kinase signalling pathways (TGFβ1/3, PDGFRα/β, IGFBP4/5/6, Wnt11). Of note, key EMT transcription factors, TWIST1/2, SNAI1/2, ZEB1/2, and stemness marker, ALDH1A3, were 2-7 times overexpressed in EMT-very high group. Furthermore, immune modulators, IL6 and IL10 were significantly upregulated and M2 macrophages were significantly more abundant in EMT-very high patients. Multiplex IHC is currently underway to confirm the abundance of TAMs and CD8-positive TRM in the two risk groups.

Conclusions: 1) The Oxford Classic-based EMT is a robust prognostic biomarker of overall survival in HGSOC, that faithfully represents the complex circuitry of pathways which are a hallmark of Epithelial to Mesenchymal Transition. 2) OxC-EMT risk stratification can identify HGSOC patients who may benefit from EMT-targeting therapies.

Reference: 1) Hu Z. Cancer Cell 2020 2) Hu Z. Clin Cancer Res 2021 3) Hollis R. Clin Cancer Res 2022

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