INVESTIGATING EPIGENOMIC INVOLVEMENT IN ACQUIRED DRUG-RESISTANCE IN HIGH-GRADE SEROUS OVARIAN CANCER

Introduction/Background* Due to advanced presentation at diagnosis and subsequent development of therapeutic resistance, ovarian cancer (OC) remains the most lethal gynaecological malignancy worldwide. High-grade serous ovarian cancer (HGSOC) is the predominant OC subtype observed in the clinical setting, and approximately 80% of women eventually develop therapeutic resistance to the standard platinum therapy regimen. The aim of this study is to understand how the epigenomic events unfold during acquired-drug resistance in HGSOC patients.

Methodology A HGSOC publicly-available dataset was used to explore alterations between primary platinum-sensitive samples (n=32) and recurrent acquired resistant samples (n=28). Results derived from methylation (HM450K array) and gene expression (RNAseq) analysis were further investigated in a paired-sample subset of the cohort (n=12). Validation, using high resolution melting and Sanger sequencing, was carried out using two pairs of matched platinum-sensitive and resistant cell lines (A2780 and UWB1.289), along with samples from pre- and post-platinum treated HGSOC patients (n=3).

Result(s)* 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 samples: PDCD1, THY1, NAKPL, C1QTNF4, DIO3, EOMES, APOBEC3A and S100A8. A detailed evaluation of the paired cohort suggested that epigenomic alterations in these genes were associated with time to relapse. Further investigation into the methylation status of these markers in paired cell lines and HGSOC patient samples revealed change in methylation dynamics (i.e. increased/ decreased methylation) across the majority of markers, in response to treatment with platinum compounds. Of the studied markers, PDCD1, NAKPL and APOBEC3, known to be prognostic markers in OC, displayed the most consistent changes across all samples. Additionally, we observed marked methylation differences between primary and metastatic samples from the same patient, highlighting the heterogeneity of the disease and the potential use of liquid biopsies to explore whole-tumour dynamics.

Conclusion* Initial investigations have identified a panel of epigenetic alterations potentially involved in HGSOC drug resistance. Dynamic methylation changes and response to platinum treatment will be further evaluated in a longitudinal plasma cell-free DNA cohort of HGSOC patients.