Methodology Patients (n=49) undergoing maximal-effort upfront-debulking surgery for advanced HGSOC had a tumour mapping of their tumour dissemination. Tumour biopsies were collected (range 4–15) from patients, and also at time of relapse (n=10 patients). DNA was extracted from tumours (5 per patient, n=49 patients plus paired relapse samples) and Illumina Human OmniExpress genotyping performed. Allele-specific recombination (HR) scores were estimated using a scarHRD algorithm, applying a cut-off >42 for HR-deficient.

Results Extensive genomic variations in CN signature exposures for different patients’ tumours were observed, including between matched primary and relapse tumours. Increased CN signature exposure scores for Signatures 2 (p=0.00017), 4 (p=0.0029) and 6 (p=0.001) correlated with poor outcome in platinum-resistant/refractory patients, increased Signature 3 correlated with favourable outcome (p=0.0018) for platinum-sensitive and no-relapse patients. Variations in HR scores were observed across the cohort with one fifth of patients presenting with a mixed HR score profile across their tumour deposits, demonstrating both HR-deficient and HR-proficient tumours within patients.

Conclusion Extensive CN variations in CN signature scores and mixed HR-deficiency/proficiency scores indicates that a single tumour biopsy does not accurately depict disseminated HGSOC biology, and therefore should not be used as the basis to derive biomarker profiles for prediction of patient treatment responses or outcomes.

Introduction/Background Despite evidence suggesting a potential role for immunotherapy in Epithelial Ovarian Cancer (EOC), initial attempts had limited efficacy. A better characterization of tumor infiltrating lymphocytes’ (TIL) immunophenotype appears crucial to deeply understand their role in anti-tumor immunity and to set the basis for their potential modulation to optimize adoptive cell therapies approaches. We extensively characterized the composition and phenotype of immune cells in EOC to identify pathways involved in limiting anti-tumor immunity.

Methodology Immune infiltrate was investigated for phenotype in 48 EOC specimens by immunohistochemistry (IHC) and flow cytometry (FC). Furthermore, the gene expression of tumor samples was evaluated with a panel of 799 immune and cancer-related genes by the Nanostring platform. FC was also used to compare T cells isolated from tumor, ascites and peripheral blood of 19 patients for memory phenotype and of the expression of multiple inhibitory receptors (IRs) and of activation markers.

Results Both IHC and FC revealed a high infiltration by T lymphocytes and myeloid cells, while B cells were scanty. High-dimensional analysis of FC data identified 2 metalusters of CD4+ and CD8+ T cells exclusively present in tumors, characterized by a CD137+CD39+PD-1+TIM-3+CD45RA CD62L+CD95+ phenotype. Gene expression profile revealed a peculiar microenvironment in samples characterized by high TIL content, with increased expression of immunity- and myeloid-related genes. Accordingly, the ligands for IRs and co-stimulatory molecules were mainly provided by myeloid rather than neoplastic cells.

Conclusion Our data suggest that EOC is infiltrated by antigen-experienced T lymphocytes displaying features of both activation and partial exhaustion, possibly driven by IRs ligands expression by infiltrating myeloid cells.
Conclusion Low ALI was associated with higher perioperative complications and poorer survival in ovarian cancer. The utility of preoperative ALI as a prognostic marker in ovarian cancer should be assessed in prospective studies.

Abstracts

A PREDICTIVE MODEL FOR DETECTION OF EPITHELIAL OVARIAN CANCER BASED ON METHYLATION LANDSCAPE

Introduction/Background More than 75% of individuals with ovarian cancer (OC) are diagnosed at an advanced stage, given that early-stage disease is usually asymptomatic. Epigenetics studies are emerging in cancer research and diagnostics with encouraging outcomes. Recent developments in large-scale DNA methylation profiling have shown that these changes are at the very early stage of carcinogenesis, indicating that the detection of such markers would drastically increase patient outcome. In OC, that would potentially represent early detection for the majority of patients. Here, we (1) investigated a large-scale methylation landscape of OC, (2) devised a predictive model based on the discovered targets, and (3) sought to validate its performance on independent external cohorts.

Methodology Fresh-frozen tissues were collected from 29 OC patients and 14 benign pelvic mass patients. Samples were submitted to global DNA methylation profiling, comprising of ~850,000 targets. For the design of the predictive model we performed: (1) univariate linear model; (2) LASSO-penalized multivariate analysis; (3) cross-validation; and (4) group assignment by centroid approach followed by principal component analysis (PCA). The predictive model was trained with our own samples and validated in 2 external cohorts.

Results We identified 21 targets that showed a clear distinction for the OC patient group, with clustering analysis showing two independent groups. Furthermore, the two main components explained 66% of the variance shown by PCA. The validation of our model in 2 independent cohorts showed classification concordance of 81.1% and 85.2%, respectively.

Conclusion Our current findings showed that OC presents an unique methylation landscape represented by a signature of 21 targets. Our predictive model algorithm showed considerable concordance with external cohorts. Noteworthy, due to the relatively small cohort used to train our model, we are currently collecting more samples to further improve its prediction efficiency, which may be relevant in diagnostic settings.

Trophoblastic diseases

ELUCIDATING MECHANISMS UNDERLYING METHOTREXATE RESISTANCE VIA QUANTITATIVE PROTEOMICS ANALYSIS OF GTN PATIENT SAMPLES AND CHORIOCARCINOMA CELL LINES: A CRUCIAL ROLE FOR SERINE METABOLISM

Introduction/Background Choriocarcinoma is an aggressive type of Gestational Trophoblastic Neoplasia (GTN). Patients with low-risk GTN following a molar pregnancy frequently commence therapy with single-agent methotrexate (MTX). Unfortunately, many develop resistance (MTX-R) and require either another single agent or more toxic combination agent chemotherapy to achieve remission. Understanding the molecular mechanisms of MTX-R may identify interventions to prevent or reverse this.

Methodology We employed proteomics profiling to identify changes that accompany MTX-R in post molar GTN patient samples and in choriocarcinoma cell lines that were either MTX sensitive (MTX-S) or resistant (MTX-R).

Results Quantitative mass spectrometry (MS) analysis revealed that the de novo serine synthesis pathway was one of the most downregulated pathways both in the MTX-R patients and in the resistant choriocarcinoma cell line. Decreased glucose-derived serine synthesis is supported by our findings that choriocarcinoma MTX-R cells have a less active glycolytic pathway.

Conclusion Upon MTX-R, choriocarcinoma cells favor redirection of serine to GSH production and this may help with combating chemotherapy-induced reactive oxygen species (ROS) accumulation and hence participate in the resistant phenotype. In contrast, MTX-sensitive cells utilize serine for nucleotide synthesis and the maintenance of proliferation. Hence, targeting upstream pathways or molecules that block the synthesis of serine in combination with or without MTX treatment could improve therapeutic response in patients with MTX resistance.