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Gynaecological cancer (2)

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Pathway analysis of gene signatures associated with platinum-based chemotherapy resistance in ovarian cancer: the big picture

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Background: Ovarian cancer is the leading cause of death from gynecological cancers in the Western world. Despite improved surgery and advances in chemotherapy the overall 5-year survival is only 30%, which is for a significant part due to platinum-based chemotherapy resistance.
We aim to gain more insight in platinum-based chemotherapy resistance mechanisms in ovarian cancer. We have therefore performed a pathway meta-analysis on seven published gene-sets associated with platinum resistance in ovarian cancer, including a study by us [1−7].
Materials, Methods and Results: A Gene Ontology analysis was done to determine which functional processes were common in the seven gene-sets. The six processes selected were cell growth and-or maintenance (84 genes), transcription (53 genes), protein metabolism (53 genes), signal transduction (45 genes), organismal physiological process (35 genes) and response to external stimulus (31 genes). With the genes belonging to these processes (i.e. focus genes), networks were generated using Ingenuity Pathway Analysis (IPA). The genes linked to most of the focus genes were labeled as key genes. Remarkably, tumor necrosis factor (TNF) was a key gene for each process, P53 for five processes and transforming growth factor beta (TGFB) for four of the processes. The same analysis with four mock data sets resulted in less keygenes and networks per process and these keygenes were found less often for the different processes indicating the validity of this approach.
Another pathway analysis was done for a subset of eight genes that showed a remarkably similar expression profile (the so-called 'extracellular matrix gene cluster') [1]. IPA generated one network with transforming growth factor beta (TGFB) as the key gene and IPA indicated that TGFB increases the expression of four of the eight focus genes.
Conclusions: TNF as well as TGFB are involved in the inflammatory response and these analyses suggest an increased presence of activated inflammatory cells and fibroblasts in the tumor microenvironment of platinum resistant ovarian carcinomas. The role of inflammation in platinum resistance and of conditions induced by inflammation such as a mutagenic environment or different ECM constitution, are subjects of future investigations.

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Correlation of the AKT/mTOR/p70S6K1 pathway and phosphorylated vascular endothelial growth factor receptor 2 in human epithelial ovarian cancer

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Background: The Akt/mTOR/p70S6K1 (Amp) pathway is activated in 55−68% of epithelial ovarian cancers. pS6 and p4EBP1 are downstream targets and presumed to be representative for the activation of Amp. pS6 has been shown to be a reliable biomarker for mTOR inhibition while p4EBP1 has been shown to be associated with tumor grade and reduced survival in ovarian cancer. VEGF-A and angiogenesis are important targets because bevacizumab as a single agent induces encouraging responses. pVEGFR2 has been shown to be a biomarker for bevacizumab treatment in inflammatory breast cancer patients. Our primary objective was to evaluate the correlation between the Amp pathway and angiogenesis. Our second objective was to evaluate whether metastatic lesions show the same expression as the primary tumor because relapses usually involve these lesions.
Material and Methods: Epithelial ovarian cancer FFPE material from 1999–2004 was collected in a tissue micro array. Immunohistochemistry was performed using pS6, p4EBP1 and pVEGFR2. An H-score was used to quantify the staining.
Results: Patients (n = 89) were FIGO stage I in 21%, stage II in 4%, stage III in 62% and 11% stage IV. 65 patients had available tissue material of both primary tumor as well as other (multiple) abdominal metastatic lesions. Considering both primary as well as metastatic lesions together, pVEGFR2 was correlated with p4EBP1 (Spearman = 0.174; $p = 0.008$). More profound correlation was found between pS6 and pVEGFR2. ($r = 0.333$; $p < 0.0001$). The correlation of pS6 and pVEGFR2 was present in tissue of primary tumors ($r = 0.279$; $p = 0.002$) but was more pronounced in tissue of metastatic lesions. ($r = 0.444$; $p < 0.0001$).
Conclusions: Although bevacizumab seems to be very active, it is at present associated with unacceptable treatment induced toxicities. Inhibiting the Amp pathway with mTOR inhibitors could potentially also influence VEGF-A mediated mechanisms in ovarian cancer with the potential of more manageable side effects. This study provides evidence that there is a relationship between the Amp pathway and pVEGFR2 in ovarian cancer. Since the correlation of activated VEGFR2 and pS6 was found on tumor cells, this suggests that VEGF-A might be a key-stimulating growth factor to the tumor cells itself by influencing downstream cell signaling proteins. The anti-tumoral activity of bevacizumab could be explained by reducing an important tumor cell growth factor besides anti-angiogenesis. Further research is necessary and ongoing.

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miRNA signatures in recurrent ovarian cancer

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Background: Conventional chemotherapy in ovarian cancer is still unsatisfactory as it ignores aspects of tumor biology during recurrence. A new class of RNA regulatory genes known as microRNAs (miRNAs) are thought to confer a novel layer of gene regulation in cancer cells. We aimed to determine whether a differential miRNA gene expression pattern exists between primary and recurrent ovarian cancers.
Materials and Methods: miRNA was isolated from 3 advanced primary and 3 recurrent serous papillary ovarian adenocarcinomas using the Ambion mirVana® miRNA isolation kit. miRNA expression levels were examined using the Applied Biosystems TaqMan® MicroRNA Assays Human Panel-Early Access Kit consisting of 180 miRNAs. miR16 and let-7a were used as endogenous controls. Quantification of primary samples was carried out relative to recurrent using the Delta Delta Ct method.Target prediction was carried out using the miRGen webserver.
Results: Differential expression patterns were identified between primary and recurrent tumours. We observed expression of miRNAs previously reported in other human cancers such as mir-155, miR-21, miR-221 and miR-222. 60 miRNAs were greater than 2-fold dysregulated between primary and recurrent specimens. 12 miRNAs were not detectable in the ovarian samples. miR-9 and miR-147 were the most differentially dysregulated genes and are predicted to target genes previously identified in our transcriptome studies. miR-147 appears to be specific for recurrence as it was detected only in recurrent specimens.
Conclusions: We report a distinct miRNA signature between primary and recurrent ovarian cancers. Some of the miRNAs identified are predicted to target dysregulated genes identified in our transcriptomic analysis of the same specimens. Three selected miRNA targets are currently being validated in an independent set of 40 primary and recurrent ovarian tumours using archival tissue. These miRNAs might represent attractive biomarkers or therapeutic targets in recurrent ovarian cancer.

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Significant antitumour activity of the novel epothilone ZK-EPO against in vitro and in vivo models of ovarian cancer

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Background: The high mortality in ovarian cancer (OC) underlines a need for more effective therapeutic options for the treatment of this disease. Epothilones are a new class of microtubule-stabilising agents that may have potential to replace taxanes in OC, and the novel epothilone ZK-EPO has shown promising activity against a range of human tumour models.