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PO-511 High miR-9 levels represent a novel prognostic biomarker to predict development of malignant meningioma

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'CD44v6 absent/low'. Patients with 'CD44v6 high' tumours that were treated with chemotherapy, in addition to surgery, displayed better OS ($p < 0.05$).

Conclusion Our study identifies CD44v6 as a novel and independent poor prognostic marker in GC with further potential use as a predictive marker for therapy response. Overall, our data supports selection of patients with high CD44v6 expressing tumours for conventional chemotherapy (in addition to surgery).

PO-510 XRCC6BP1: A NOVEL ROLE IN THE DNA REPAIR OF PLATINUM RESISTANT NSCLC CELLS

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Introduction Alterations in the DNA repair capacity of damaged cells are now recognised as an important factor in mediating resistance to chemotherapeutic agents.

Material and methods DNA Repair Pathway RT² Profiler Arrays were used to elucidate key DNA repair genes implicated in chemoresistant NSCLC cells using cisplatin resistant (CisR) and corresponding parental (PT) NSCLC cell lines generated in our laboratory. DNA repair genes significantly altered in CisR cells were validated at the mRNA and protein level. The translational relevance of differentially expressed genes was examined in a cohort of chemo-naïve matched normal and tumour lung tissues from NSCLC patients. Loss of function studies were carried out using siRNA technology. The effect of XRCC6BP1 gene knockdown on apoptosis was assessed by FACS. Cellular expression and localization of XRCC6BP1 protein and gH2AX foci in response to cisplatin were examined by immunofluorescence (Cytell). To investigate a role for XRCC6BP1 in lung cancer stem cells, Side Population (SP) studies were used to characterise stem-like subpopulations within chemoresistant cells. XRCC6BP1 mRNA analysis was also examined in ALDH1⁺ and ALDH1⁻ subpopulations. Immunohistochemistry analysis was carried out in resected lung tumour tissues and XRCC6BP1 expression was correlated with survival and other clinicopathological parameters.

Results and discussions We identified a number of critical DNA repair genes that were differentially expressed between PT and CisR NSCLC cells. XRCC6BP1 mRNA and protein expression was significantly increased in H460 CisR cells relative to their PT counterparts. Relative to matched normal lung tissues, XRCC6BP1 mRNA was significantly increased in lung adenocarcinoma patients. Gene silencing of XRCC6BP1 induced significant apoptosis of chemoresistant cells and reduced their DNA repair capacity. Immunofluorescence studies showed an increase in XRCC6BP1 protein expression and gH2AX foci in CisR cells. SP analysis revealed a significantly higher stem cell population in resistant cells, while XRCC6BP1 mRNA expression was considerably increased in SKMES-1, H460 and H1299 ALDH1⁺ CisR cells compared to ALDH1⁻ cells. IHC scoring of XRCC6BP1 showed that lung cancer patients with high expression had worse survival outcomes.

Conclusion Our data highlight the potential of targeting components of the DNA repair pathway in chemoresistant lung cancer, in particular XRCC6BP1, either alone or in combination with conventional cytotoxic therapies such as cisplatin.

PO-511 HIGH MIR-9 LEVELS REPRESENT A NOVEL PROGNOSTIC BIOMARKER TO PREDICT DEVELOPMENT OF MALIGNANT MENINGIOMA

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Introduction Meningioma is the most common primary tumour affecting the central nervous system; it is classified as benign (WHO I, ~80%), atypical (WHO II, ~15%–20%) and anaplastic/malignant (WHO III, ~1%–3%). The 3 year recurrence rate in WHO I meningioma is estimated in about 50% and it is much greater in WHO II and III tumours. MicroRNAs (miRNAs) represent a large class of small RNAs driving regulation of gene expression at post-transcriptional level and playing a role in cell proliferation, differentiation, apoptosis and carcinogenesis. Several studies showed that miRNAs are involved in tumour progression and therefore proposed as diagnostic tools. Here, we evaluated miRNAs signature in meningioma to identify novel biomarkers of tumour progression.

Material and methods Meningioma (MN) specimens were collected from consented patients, according to the ethics. The 96-miRNA profiling was performed using the QuantimirTM Cancer MicroRNA qPCR Array (System Biosciences, UK) following the instructions of the supplier. Validation studies were achieved using TaqMan MicroRNA reagents (Applied Biosystems). Bioinformatic analysis was done using the NormFinder software and *in silico* studies were performed using the following datasets for putative miRNA targets: TargetScanHuman7.1, DIANATOOLS microT-CDS, mirDIP and the UTRdb tool. Probability (p) values were calculated using the Student's t-Test, led by the GraphPad Prism 5.01 ($p < 0.05 \pm \text{SEM}$).

Results and discussions We established a new miRNA dataset by identifying six miRNA signatures ($p < 0.01$) differentially regulated in benign versus malignant meningioma cells (miR-9, -10b, -125b, -143, -145 and -199). Validation studies by qPCR confirmed that the miR-9 was upregulated in malignant KT21-MG1 cells (10.71 folds; Log₂ scale, $p = 0.0006$) and WHO III tissues (3.75 folds versus WHO I=0, Log₂ scale, $p = 0.044$). Finally, highly stringent *in silico* studies suggested that the miR-9 targets and downregulates the ubiquitin-protein ligase E3C (UBE3C), as confirmed by proteomic analysis in malignant KT21-MG1 and IOMM-Lee cells.

Conclusion In this study, we identified the miR-9 as significantly upregulated in WHO III tumour-derived meningioma cells and tissues when compared to lower grades. Since miR-9 targets the ubiquitin-protein ligase E3C, involved in the ubiquitin-proteasome pathway and therefore regulating protein homeostasis, this protein, together with miR-9, could represent potential novel diagnostic and/or prognostic biomarkers in meningioma.

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