OFP-18-004

Loss of Raf-1 Kinase Inhibitor Protein (RKIP) promotes Epithelial Mesenchymal Transition (EMT) and correlates with aggressive phenotype in Pancreatic Ductal Adenocarcinoma (PDAC)

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Objective: RKIP has emerged as a significant metastatic suppressor in a variety of human cancers and is known to inhibit the Ras/Raf/MEK/ERK signaling. By suppressing the activation of NFkB/SNAIL circuit, RKIP can regulate the induction of EMT. The aim of this study was to evaluate RKIP expression and to determine its association with clinic-pathological features, including EMT in form of tumor budding in PDAC.
Method: Staining for RKIP was performed on a multipunch Tissue Microarray (TMA) of 120 well-characterized PDACs with full clinicopathological, follow-up and adjuvant therapy information. RKIP-expression was assessed separately in the main tumor body and in the tumor buds. Cut-off values were calculated by receiver operating characteristic curve analysis.
Results: RKIP expression was lost in 61.4 % of the PDACs and was significantly lower in the tumor buds compared to the main tumor body ($p<0.005$). RKIP loss in the tumor was associated with higher tumor grade ($p=0.0389$) and high-grade peritumoral budding ($p=0.0118$). RKIP loss in the buds was associated with increased T stage ($p=0.035$). No correlation with M- and N-stage or patient survival was found.
Conclusion: Loss of RKIP correlates with aggressive features in PDAC, especially characterized by the presence of EMT in form of tumor budding.

OFP-18-005

Correlation of mitotic grade and Ki-67 index grade between histological and scrape cytological specimens in pancreatic neuroendocrine tumor

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Objective: The purpose of this study was to correlate mitotic grade (MG) and Ki67-index grade (KG) between histological and scrape cytological specimens in 61 resected primary pancreatic neuroendocrine tumors (P-NETs).
Method: Ki67 index was calculated as a percentage of 2000 cells in 'hot spots' on histological specimens and as a percentage of 100, 500, 1,000, and 2,000 cells in 'hot spots' on scrape cytological specimens. Mitotic count was calculated in the high-density area of mitoses per 10 high power fields by scanning 50 fields on histological specimens and 10, 20, or 50 fields on scrape cytological specimens. MG and KG were classified according to ENETS/WHO grading system.
Results: Kappa values of scrape cytological KG per 500, 1000, and 2000 cells showed a substantial agreement with histological KG, whereas KG per 100 cells only showed a fair agreement. Furthermore, when the cases were subdivided into KG1-2 and KG3, kappa value showed an almost perfect agreement. In contrast, kappa values of scrape cytological MG showed a fair agreement with histological MG.
Conclusion: Our results indicate that scrape cytological KG, determined in a small number of cells (e.g., 500 cells), accurately predicts histological KG, whereas scrape cytological MG does not predict histological MG.

OFP-18-006

The CD8/CD45RO immunoscore in biopsy specimens of colorectal cancer predicts histopathologic features of the matched resection specimen and survival outcome

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Objective: Reliable biomarkers based on pre-operative biopsies of colorectal cancer (CRC) are missing. We hypothesize that an immunoscore of CD8+ T-effector and CD45RO+ memory T-cell infiltrates in biopsies may predict histopathological features and survival outcome of CRC patients.
Method: Intraepithelial and stromal (s) CD8+ and CD45RO+ T-cells were quantified in 5 high-power-fields each of the highest density of infiltration in biopsy specimens of 130 well characterized CRC patients. Using Classification and Regression Tree (CART) analysis, CD8+ and CD45RO+ infiltrates in each zone were assessed for clinical relevance.
Results: High total (t) numbers of infiltrating CD8+ T-cells in biopsies strongly predicted the absence of nodal metastasis ($p=0.0182$) and lymphatic invasion ($p=0.0201$) in the matched resection specimen. High numbers of sCD45RO+ T-cells predicted earlier T-stage ($p<0.0001$), lower tumor grade ($p=0.0223$) and absence of distant metastasis ($p=0.0177$). 100 % specificity and PPV for the prediction of pN was reached by combined analysis of tCD8 and tCD45RO. Strong immune infiltration in biopsies was highly prognostic [tCD8: HR (95 %CI)=0.29 (0.1–0.7); $p=0.0061$; sCD45RO: HR (95 %CI)=0.43 (0.2–0.9); $p=0.0364$].
Conclusion: An immunoscore of CD8 and sCD45RO in pre-operative biopsy specimens allows prediction of full TNM-stage of the matched resection specimen and survival outcome in the pre-operative setting.

OFP-18-007

Hypermethylation of ZEB2 represents a novel mechanism of colorectal cancer progression and is a highly unfavourable prognostic factor in KRAS wild-type tumors

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Objective: A majority of colorectal cancers exhibit de-regulation of WNT pathway signaling. This may include loss of E-cadherin expression through transcriptional regulation of ZEB1 and ZEB2. Here, we investigate the methylation status and prognostic effect of ZEB1 and ZEB2 in colorectal cancer.
Method: 77 primary colorectal cancers from patients with full clinicopathological and survival time data underwent methylation analysis for ZEB1 and ZEB2, and mutational analysis of KRAS and BRAF using pyrosequencing.
Results: ZEB1 was unmethylated in all cases. Frequent methylation of ZEB2 was observed (average 32.6 %; range 1–99 %). ZEB2 hypermethylation was significantly greater in patients with KRAS wild-type tumors ($p=0.0397$) and BRAF mutated cancers ($p=0.055$). Stratified by KRAS status, hypermethylation of ZEB2 in wild-type tumors was highly associated with more advanced pT stage ($p=0.0463$), lymph node positivity ($p=0.0032$), distant metastasis ($p=0.0192$), venous invasion ($p=0.0193$), lymphatic invasion ($p=0.0025$) and unfavorable survival ($p=0.0155$; HR (95 %CI): 3.2 (1.2–8.6)), but not with tumor budding. No associations were observed in KRAS mutated cases.
Conclusion: These findings underline a role for ZEB2 hypermethylation as a novel mechanism of colorectal cancer progression. Moreover, hypermethylation of ZEB2 identifies a highly aggressive subgroup of colorectal cancer patients in the context of a KRAS wild-type background only.

OFP-18-008

Investigation of IL23 (p19, p40) and IL23R highlights nuclear IL23p19 expression as a marker of indolent tumor features and favorable outcome in colorectal cancer patients

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Objective: IL23 is involved in chronic inflammation but its role in cancer progression is not fully elucidated. Here we characterize IL23 subunits p40, p19 and IL23 receptor (IL23R) in the normal-adenoma-carcinoma-metastasis cascade of colorectal cancers and their relationship to clinicopathological and outcome data.
Method: Immunohistochemistry for IL23R, IL12p40, IL23 and IL23p19 (monoclonal) was performed on a multi-punch tissue microarray ($n=213$ patients). Expression differences between normal-adenomas-cancers-lymph nodes were evaluated. Correlation with clinicopathological and outcome data was undertaken. Results were validated on an independent cohort ($n=341$ patients).