all proteolytic factors except uPA, PAI-1 and KLK13; there were substantial upward trends in uPA, PAI-1, and KLK5 from primary tumor to omentum. In univariate analysis, larger level differentials of uPA, KLK5, 6, 7, 10 were significantly associated with disease progression in the cohort as a whole, as was residual tumor mass. Higher level differentials of uPA, KLK5, 6, 7, 8, 10, 11 were strongly associated with residual tumor mass >10 mm. In the subcohort of patients with residual tumor mass <10 mm, level differentials of KLK5, 6, 7, 8, 10, 11 had a significant impact on tumor progression, whereas those of uPA, PAI-1, and KLK13 did not. Hence, the observed impact of level differentials in KLK5, 6, 7, 10 on tumor progression was not simply attributable to their association with surgical success. Positive level differentials of uPA and KLK10 were also associated with poorer overall survival, as was presence of residual tumor mass. No significant association of level differentials of the proteolytic factors assessed with response to first-line chemotherapy was observed.
Conclusion: Since protein level differentials between primary tumor and omentum metastasis of the assessed proteolytic factors measured at initial presentation impact both surgical outcome and survival in advanced ovarian cancer, these measurements could support clinical decisions on surgical and systemic therapy or help in patient selection for novel targeted therapies.

PP29

Tissue factor expression in colorectal cancer: a surrogate for KRAS and p53?

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Background: Tissue factor (TF), a glycoprotein involved in physiologic and cancer-related thrombosis, has been shown to be associated with mutated (mt) KRAS in colorectal cancer (our unpublished data). Interestingly, recent data indicate that p53 mutations confer sensitivity to EGFR-inhibitors in metastatic colorectal cancer. In the present study we address the question of a potential relation of TF expression to the mutational status of both KRAS and p53. Since overexpression of amphiregulin and epiregulin, both EGFR-ligands, are known to be associated with sensitivity to EGFR inhibitors, we were also analyzing whether these ligands might modulate TF.
Materials and Methods: An established microarray database (AFFYMETRIX; U133) of colorectal cancer genotyped for KRAS, BRAF and p53 was analyzed for expression of TF, amphiregulin (AREG) and epiregulin (EREG). Expression analysis was correlated to the underlying mutation of the tumor sample using a two-sample t-test. Correlation between expression levels of two genes was evaluated using Pearson correlation.
Results: A total of 161 primary colorectal cancer cases were analyzed. 93 cases were wild-KRAS, 52 mutated-KRAS and 17 mutated-BRAF; p53 status was available in 121 tumors (43 wt-p53; 78 mut-p53). Tumor samples with the genotype mt-KRAS/wt-p53 ($n = 10$) had higher levels of TF than those with wt-KRAS/mt-p53 ($n = 56$) ($p = 0.008$). TF expression between mt-KRAS/mt-p53 ($n = 22$) and wt-KRAS/wt-p53 ($n = 33$) was not significantly different. When comparing TF expression between wt-KRAS/mut-p53 with wt-KRAS/wt-p53, TF expression was trending towards lower levels in wt-KRAS/mut-p53 ($p = 0.284$). Studying expression of AREG as well as EREG between wt-KRAS and mt-KRAS patients, AREG and EREG were significantly downregulated in mt-KRAS ($p = 0.001$). Correlation of TF expression to AREG and EREG expression restricted to samples with wt-KRAS showed an inverse association with EREG ($p = 0.023$) and AREG(215564_at) ($p = 0.039$), but not AREG(205239_at) ($p = 0.42$).
Conclusion: We report a stepwise increase of Tissue Factor in colorectal tumors with lowest TF levels in wt-KRAS/mt-p53 and highest levels in mt-KRAS/wt-p53; no direct correlation with EGFR-ligands AREG and EREG was observed. Immunohistochemical studies to evaluate the role of TF as surrogate marker for KRAS/p53 status are ongoing.

PP53

Hakai − a novel tissue based tumour progression marker

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Background: The transition from adenoma to carcinoma has been linked to the disruption of cell-cell contacts and with the loss of E-cadherin, a membrane protein with a critical function in the formation of adherens junctions. Although many proteins are involved in the establishment of cell-cell contacts, E-cadherin is perhaps the most important protein for the formation of tight, compact intercellular adhesions. E-cadherin is regarded as a tumour suppressor gene and its loss as a predictor of poor prognosis in colon cancer.
In 2002, Hakai was identified as a novel E3 ubiquitin-ligase, related to Cbl-family ubiquitin ligases, that acts on the E-cadherin complex and mediates its ubiquitination, endocytosis and degradation via lysosomes, thereby altering cell-cell adhesions.
The loss of E-cadherin at the surface of cancerous cells correlates with the process of invasion and metastasis. The excessive internalization or degradation of E-cadherin, such as when Hakai is over-expressed, may achieve similar results, raising the possibility that Hakai may participate in tumour progression and metastasis. Indeed, Hakai can regulate the proliferation of cell cultured cells in an E-cadherin-independent manner. Moreover, Hakai induces anchorage-independent cell growth, further underscoring its oncogenic potential and preliminary results show that the expression is often enhanced in human colon and gastric adenocarcinomas. The main objective of this study is to determine the potential of Hakai as a tumour progression marker in human colon tissues.
Materials and Methods: We have analyzed the expression of Hakai in different normal human and colon cancer tissues by immunohistochemistry using Hakai (2498) antibody. We have analyzed 15 normal human mucosa and the same number of grade I, grade II and grade III of tumour differentiation stage. We have correlated the tumour differentiation stage with the expression level of Hakai protein by immunohistochemistry
Results: Preliminary results indicate that there is an enhanced expression of protein level in tumour samples than in normal mucosa. We have obtained more than 3-folds increase of enrichment of Hakai protein in tumour tissues versus normal mucosa analyzed. We haven't found any significative correlation between every differentiation stage and Hakai expression level.
Conclusion: These results suggest that Hakai can be used as a novel tumour marker in colon tissues and the overexpression detected in tumour samples is not related to tumour differentiation stage.

PP119

VEGF polymorphisms as predictors of bevacizumab efficacy in metastatic colorectal cancer

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Background: During cancer processes, VEGF sustains cancer neoangiogenesis and is largely released by normal cells under cancer mediator stimulation. The anti-VEGF antibody bevacizumab (B) has demonstrated relevant efficacy in metastatic colorectal cancer patients (MCRC pts) when given in combination with the chemotherapeutic regimen FOLFIRI (F). The aim of this study was to evaluate potential influence of germline VEGF gene polymorphisms (VGPs) on B efficacy.
Materials and Methods: 55 MCRC pts (40 treated with F+B, 15 with F alone; M:F 31:24, median [m] age 62 years) with available blood sample for genotyping entered the study between November 2005 and July 2008. 9 VGPs (7 of which single nucleotide polymorphisms) within the 5′UTR/promoter region spanning from nt −2713 to nt −585 were evaluated. Primary endpoint was median progression free survival (mPFS), secondary endpoints were radiological response rate (RR) and overall survival (OS).
Results: 5 VGPs were strongly linked to each other and, among pts receiving F+B, the 17 pts with the homozygotic haplotype for these 5 VGPs: −2578 C/C, −1512 18base pairs deletion/deletion, −1451 C/C, −1411 repeats 5G/5G, −460 T/T, had significantly longer mPFS compared to the other 23 F+B treated pts, 15.4 v 9.0 months (mo), respectively, HR 0.38, p 0.02. Also the VGPs −152 (G/G v G/A + A/A) and −1154 (G/G v G/A + A/A) were significantly associated with mPFS in F+B pts: 15.4 v 8.9 mo, HR 0.28, p 0.01 and 16 v 9.8 mo, HR 0.43, p 0.03, respectively. OS was not significantly influenced by any of the investigated VGPs in patients receiving F+B. With regard to RR, among all the VGPs only the −634 VGP was significantly associated with response to F+B, RR for G/G vs. G/C + C/C = 64% vs. 14%, Fisher's test $p = 0.03$. All the VGPs did not significantly influence the outcomes of F alone treated patients.
Conclusion: Germline VGPs of the 5′UTR/promoter region may help identify patients more sensitive to anti-VEGF agents.