differentiation and the control of liver-specific gene expression is attributed to hepatocyte nuclear factors (HNF), the role of this class of transcription factors in hepatocarcinogenesis is relatively poorly understood.
Using the experimental model of mouse one-step HCC progression in which a slow-growing differentiated tumor (sgHCC) rapidly gave rise *in vivo* to a highly invasive dedifferentiated fast-growing variant (fgHCC), we have investigated the fundamental mechanisms underlying HCC progression and the role of HNFs in this process.
The progression from sg to fgHCC variant was accompanied by a complete loss of cell polarity, a decrease in cell-cell and cell-matrix adhesion, activation of telomerase, extinction of liver-speci?c gene expression, ability to proliferate rapidly in the culture, invasion and metastasis. These alterations were coupled with a reduced expression of several liver transcription factors including HNF4, a nuclear receptor essential for hepatocyte differentiation. Studies of the collection of chemically induced mouse HCCs of independent origin and human HCC clinical samples revealed strict correlation of HNF4 expression with tumor differentiation status.
Forced expression of HNF4 in cultured fgHCC cells partially re-established epithelial morphology, hepatic gene expression, induced the decrease of proliferation rate and dramatically inhibited tumor growth *in vivo*. Thus HNF4 reexpression can promote the reversion of invasive HCC toward a less aggressive phenotype.
HNF4 promoter was found to be inactive in fgHCC, providing the strong evidence for the existing of HNF4 upstream mechanisms responsible for tumor progression. Some candidate genes were identified by microarray analysis of gene expression profiles in one-step HCC progression model. Investigation of the interplay of HNFs network with signaling pathways conducting the control of cell proliferation and morphology is now in progress.
These data indicates that deregulation of tissue-specific transcription regulation network might be a crucial step of epithelial tumors progression.
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755 POSTER

Role of interleukin-1 alpha in hepatic metastatic potential in pancreatic carcinoma cells

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To study the mechanism of gene expression during formation of hepatic metastasis in pancreatic cells, we performed differential display assay of two pancreatic cell lines with highly metastatic potential (BxPc-3 and Sw1990) and two cell lines with non-metastatic potential (Capan-2 and Mia PaCa-2).
There were 39 different shifts in expression, 24 in the highly metastatic group and 15 in the non-metastatic group. Further DNA sequencing, homology research, Northern blotting, and/or reserve transcription-PCR results indicated that interleukin-1 alpha was among those up-regulated in highly metastatic group. An interleukin-1 receptor antagonist was also found to reduce hepatic metastasis in an intrasplenic metastatic assay using nude mice. Antisense cDNA of interleukin 1 alpha into SW1990 caused loss of metastatic potential in nude mice, while interleukin-1 alpha transfection into MIA PaCa-2 generated metastatic potential in nude mice. EMSA assay also demonstrated NF kappa B activation in highly metastatic carcinoma cells. These results indicate that interleukin-1 alpha and activation of the NF kappa B play an important role in the acquisition of metastatic potential in pancreatic cells.

756 POSTER

Interleukin 1 B gene polymorphisms and gastric adenocarcinoma in Oman – Preliminary results

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Gastric cancer (GC) is the most common malignancy in Sultanate of Oman. Interleukin 1beta (IL-1B) gene polymorphisms have been associated with increased risk of GC in Caucasian, Asian and Hispanic populations. No previous studies examined its role in Arab population. We tested the association between IL-1B-31, IL-1B-3954, IL-1RN-(2018) polymorphisms and GC in Omani Arab patients.
Method: Genomic DNA was extracted from peripheral blood of 175 healthy blood donors, 75 gastric cancer patients. The DNA samples were analysed using TaqMan real-time polymerase chain reaction and 5' nuclease assay. The frequency of carriage of the pro-inflammatory alleles were IL-1B-31*C, IL-1B-3954 *T, and IL-1B-RN*C were 76%, 42.3%, and 33.4% respectively in GC patients compared to 67%, 47.8%, and38.2% respectively in the controls. There was no statistical association between carriage of the pro-inflammatory alleles and gastric cancer; IL-1B-31*C (odds ratio [OR] – 1.53, 95% confidence interval [CI]-0.79–2.97, p = 0.2), IL-1B-3954 *T (OR – 1.56, 95% CI-0.56–4.5, p = 0.4), and IL-1B-RN*C (OR – 0.8, 95% CI-0.45–1.47, p = 0.5).
Conclusion: In these preliminary results, there is no association IL-1B-31, IL-1B-3954, IL-1RN-(2018) polymorphisms and GC in Omani Arab patients.

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Analysis of C-KIT mutations in gastrointestinal stromal tumors

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Gastrointestinal stromal tumors (GIST) is the unique model for the molecular based diagnostics, prognosis and treatment of gastrointestinal mesenchymal malignancies. GISTs typically express high levels of the KIT-receptor and carry activating C-KIT mutations, primarily of exons 11 and 9. We analysed C-KIT mutations by direct sequencing in 43 DNA samples from 36 GIST patients and 6 DNA samples from 5 leiomyomas and one leiomyosarcoma. All GISTs were CD117 positive and 65% GISTs were CD34 positive. Mutations of 11 exon were found in GISTs of stomach (68%, 17/25) and intestine (36%, 4/11). The most frequent deletions were located in the region of 551–563aa. with mutations of one of 557, 558 or 559 aminoacid. We did not found any correlation between this mutation and level of malignancy of GIST. In four GISTs with low malignancy we found insertions of different size in the region of 576–585aa of 11 exon. Point mutations of 11 exon were rare. Mutations of 9 exon (duplications of 502–503aa) were found exclusively in GISTs of intestine (45%, 5/11). Such tumors were CD34 negative, rather agressive and had poor prognosis. All DNA samples from 5 leiomyomas and one leiomyosarcoma were CD117 negative without c-KIT mutations in 11 and 9 exons. We conclude that the type and location of C-KIT mutation may be the additional parameter for predicting prognosis and effectiveness of treatment for GISTs.

758 POSTER

Decreased xanthine oxidoreductase is a predictor of poor prognosis in early stage gastric cancer

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Background: Xanthine oxidoreductase (XOR) is a key enzyme in the degradation of DNA, RNA and high energy phosphates. Alterations in XOR expression have been reported in experimental tumorigenesis. We showed previously that breast **cancer** is accompanied by a decrease in XOR expression in about half of the cases, and loss of XOR independently identifies breast cancer patients with unfavorable prognosis. The purpose of the present study was to assess the clinical relevance of XOR in gastric **cancer**.
Materials and Methods: In this study we determined the XOR levels by immunohistochemistry in tissue microarray specimens of 337 patients with gastric **cancer** and assessed the relation between XOR expression and a series of clinicopathologic variables as well as disease specific survival.
Results: XOR expression was moderately decreased in 41% and undetectable in another 14% of the tumors as compared to the corresponding normal tissue. Decreased XOR was associated with advanced stage, deep tumor penetration, diffusely spread tumor location, positive lymph node status, large tumor size, non-curative disease, cellular aneuploidy, high S-phase fraction and high cyclooxygenase-2 expression, but not with p53 expession or Borrmann classification. Downregulation of XOR was associated with unfavourable outcome, and the cumulative five year gastric specific survival in patients with strong XOR expression was 47% compared to 22% in those with moderate-to-negative expression ($P < 0.0001$). This was also true in patients with stage I-II ($P = 0.0124$) and lymph node negative ($P = 0.018$) disease as well as in patients with smaller ($\leqslant 5$ cm) tumors ($P = 0.02$).
Conclusions: Our data suggest that XOR expression in gastric cancer might be a new marker for a more aggressive gastric cancer biology, similar to that as previously reported for breast cancer.