Inhibitory effect of HT10 on VEGF-mediated KDR phosphorylation in HUVECs was evaluated. VEGF165 dependent Matrigel plug assay was performed to verify the antiangiogenic potential of HT10 as a VEGF165 inhibitor. Finally, tumor growth inhibition effects of HT10 in SCC7 and the survival rate of animal models was investigated. Moreover, MDA-MB231 xenograft mouse model was additionally used to confirm the therapeutic effect of HT10 in human cancer cell lines.
Results: HT10 binds to VEGF strongly and inhibit VEGF dependent KDR phosphorylation. The results of Matrigel plug assay bolstered the action of HT10 as an antiangiogenic agent inhibiting VEGF165. HT10 showed a significant tumor growth inhibition potential on SCC7 with an elongated survival rate. HT10 also delayed tumor growth in MDA-MB231 human breast cancer cell lines.
Conclusions: HT10 showed significant antiangiogenic potential and tumor growth inhibitory effect by neutralizing VEGF165 functions.

60 POSTER

Expression of a gastrin transcript in gastrointestinal cancer cells which allows maintenance of expression in hypoxia

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Background: The gastrointestinal (GI) hormone gastrin is known to promote GI cancer progression by promoting angiogenesis and cell survival pathways. Since expression of a number of genes involved in angiogenesis are controlled at the translational level through the presence of an internal ribosome entry site (IRES) within the 5′ untranslated region (5′UTR) of the transcript, we investigated the possibility that gastrin expression in GI tumours may be regulated at the translational level.
Methods: The sequence within the 5′UTR of gastrin mRNA from pancreatic GI cancer cells was investigated by RNA ligase-mediated Rapid Amplification of cDNA Ends (RACE) and compared with the transcript described in Ensembl. Expression of two alternative gastrin transcripts was investigated in a panel of GI cancer cells by reverse transcriptase PCR (RT-PCR) using specific primers. To investigate its ability to act as an IRES, sequence from the 5′UTR of the gastrin transcript was cloned into a dicistronic vector upstream of firefly luciferase and the IRES-dependent firefly luciferase signal was measured relative to that of a constitutively-expressed cap-dependent renilla luciferase, following transfection into GI cancer cells.
Results: The gastrin transcript identified in pancreatic cells had a 5′UTR with sequence that did not match the transcript described in Ensembl. Instead, transcription is initiated approximately 100bp upstream of the translation start site at a site within the region designated at the gene's first intron. The sequence has a high GC content (60.7%) and includes an AUG codon upstream of the translation start-site. This transcript is expressed in a panel of GI cancer cells including cells of pancreatic, gastric, colonic and oesophageal origin. Sequence from the 5′UTR of the transcript showed IRES activity in GI cancer cells under basal conditions and there was induction of the IRES-driven firefly luciferase signal induction following exposure of the cells to hypoxia or mitomycin C (up to 25-fold) which was paralleled by down-regulation of translation of the cap-dependent renilla luciferase.
Conclusion: These data suggest that expression of this gastrin transcript within GI cancer cells, driven from an alternative promoter, contains an IRES that maintains expression of gastrin peptides under conditions when normal translational mechanisms are inactive, promoting angiogenesis and cancer cell survival.

61 POSTER

Contrast enhanced perfusion CT (CEPCT) predicts early response of sunitinib in renal cell carcinoma (RCC) patients

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Background: Sunitinib treatment remains the mainstay of therapy for most pts. with metastatic RCC. Objective response to treatment is often assessed after repeated administration of the drug by measurement of tumor size in CT. However, these morphological changes may not necessary reflect the biological activity of sunitinib and its detection may provide additional guidance to evaluate clinical activity throughout the course of sunitinib. We assume that biological effects precede morphological changes, which can be detected by CEPCT. The aim of the study was to pilot changes of tumor angiogenesis in comparison to morphological response according to RECIST criteria.
Materials and Methods: 9 patients with metastatic RCC were evaluated retrospectively by CEPCT during October 2007 to May 2008. All pts. were treated with 50 mg sunitinib d1−28 q6wk. One patient received re-instigation of therapy after prior complete response to sunitinib, all other patients were treatment-naive. CEPCT was performed at the end of every 2 cycles. 2 pts. additionally received early CEPCT at the end of the first cycle. Tumor angiogenesis was assessed by perfusion CT measurements.
Results: The median age of patients was 69 years, 8 pts. were male, 1 was female. The median time on treatment was 108+ days. All pts. are currently receiving sunitinib treatment. Tumor assessment was too early in 2 pts., all other pts. received repeated CT-scans. According to RECIST 2 partial remissions (PR) and 5 disease stabilizations (SD) were determined. Assessment of contrast enhancement measures and tumor size according to RECIST revealed similar response in treated pts. Decrease of tumor perfusion was detected after the first course of sunitinib, and may allow an earlier assessment of tumor response than therapy monitoring according to RECIST criteria. Updated results will be presented at the meeting.
Conclusions: CEPCT detects early changes in blood perfusion of the tumor, which may precede objective tumor response during the latter course of treatment. Changes may be seen as early as after 28 days of treatment. CEPCT may represent a simple method, which cost-effectively monitors biological response of sunitinib treatment.

62 POSTER

Expression and functional activity of interleukin-8 receptors on human malignant melanoma cells

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Background: Recent evidence indicates that cancer cells express chemokin receptors which signaling is crucial for tumor proliferation, migration and angiogenesis. In the present study, we have examined the autocrine/paracrine role of Interleukin-8 (CXCL8) in melanoma growth, migration and invasion by analyzing the expression and functional significance of CXCL-8 receptors, CXCR1 and CXCR2.
Materials and Methods: The expression of CXCL-8 was examined in a panel of human malignant melanoma cells by using western blot and enzyme-linked immunosorbent assay. Expression of CXCR1 and CXCR2 was detected by flow cytometry. Cell Proliferation (Colorimetric assay), Cell Migration and Invasion (Boyden Chamber) were performed in presence or absence of anti-CXCR2, anti-CXCR1 and anti-CXCL8 neutralizing antibodies.
Results: Five out of six melanoma cell lines tested produced very different levels of CXCL-8 (ranging from undetectable to up to 50 ng/106 cells). Highly metastatic M20 and A375SM cells expressing similar levels of CXCR1 and CXCR2, but different levels CXCL-8 protein were chosen for all experiments. Treatment of M20 cells, expressing very low levels of CXCL-8, with exogenously added human recombinant CXCL-8 significantly enhanced their proliferation, on the contrary A375SM cells, producing high amount of CXCL-8 protein, were not responsive to exogenously CXCL-8 exposure. We found that cell proliferation of unstimulated A375SM cells and CXCL-8-stimulated M20 cells was significantly reduced in presence of neutralizing antibody against CXCL-8 when compared to cells cultured with medium alone or control antibody, confirming the autocrine/paracrine role of CXCL-8 in melanoma cell proliferation. Furthermore, we investigated which receptor(s) mediated the functions of CXCL-8 in melanoma cells. We observed reduced migration and invasion of M20 and A375SM melanoma cells treated with anti-CXCR2, but not anti-CXCR1 neutralizing antibodies, as compared to controls.
Conclusions: The findings confirm the autocrine/paracrine role of CXCL-8 in melanoma cell proliferation and suggest that constitutive expression of CXCR2 plays an important role regulating the CXCL-8-mediated invasive behaviour of human malignant melanoma cells.

63 POSTER

Response of papillary cell carcinoma to antiangiogenics: a retrospective analysis

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Background: Papillary cell carcinoma is a rare subtype of renal cell carcinomas as it accounts for 7 to 14% percents of them. For metastatic PCR (mPCR), cytokines and chemotherapy were evaluated on small studies and median overall survival time range from 5.5 to 8 months.