immunostaining was not an independent prognostic factor of treatment response in the group treated with radiotherapy.
Conclusion(s) Down-regulation of MGMT expression occurs in oligodendroglial tumors since early phases. Low or negative MGMT protein expression at similar proportions in low and high grade tumors strongly suggest that this alteration could play a pathogenetic role in the initiation of oligodendroglial neoplastic development. - MGMT protein downregulation prevents DNA repair, allowing the accumulation of mutations that could lead to neoplastic transformation as a result of the impairement of a fundamental genomic protective pathway.

P4.105
mRNA expression of collagen V gene increased in pulmonary fibrosis of systemic sclerosis

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Background Our previous studies done with animal model of systemic sclerosis (SSc) had proven that fibrosis was due to increased amount of abnormal collagen type V (Col V). We propose to analysis Col V in lung tissue of SSc patients.
Methods We examined the amount of collagen V and mRNA chains expression using immunofluorescence, Real-time PCR and computer morphometric analysis in 15 open lung biopsies of patients with SSc. The pulmonary function tests were analyzed and correlated with collagen amount and PCR chains expression. Normal lung tissue was obtained from 8 individuals who had died from traumatic injuries.
Results Immunofluorescense showed abnormal dense thick Col V bundles in the interstitium and histomorphometry revealed higher amount of distorted Col V fibers, when compared with control group. In SSc patients there were increased [α1(V)] and [α2(V)] mRNA chains expression when compared with control, but [α2(V)] was proportionally raised compared to control group. High levels of collagen V were inversely associated to VC (r=-0.72; p= 0.002), FCV (r=-0.76; p<0.001) and FEV1 (r=-0.89; p< 0.001) pulmonary function tests.
Conclusion(s) We conclude that abnormal Col V fibers are overproduced in SSc patients and it could plays an important role in the pathogenesis of SSc, since this molecule regulates tissue collagen assembly. This aberrant histoarchitecture observed in SSc can be related to over-expression of [α2(V)] gene of unknown origin. Financial supported: FAPESP, CNPq.

P4.106
Ursodeoxycholic acid induces apoptotic death through activation of ERK1/2 and A-SMase in gastric cancer cells

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Background Ursodeoxycholic acid (UDCA) is well recognized as its cyto-protective and anti-apoptotic role, and suppressor of cholestatic liver diseases and colorectal cancer development. Presently, we demonstrate that UDCA induces cell death in human gastric cancer cells.
Methods We investigated the effect of UDCA on SNU601 and SNU638 cells through the evaluation of molecular mechanism of cell death as well as morphologic changes.
Results UDCA triggered cell death mainly through apoptosis with low level of autophagic death in both cells. Upon UDCA exposure, the number of clone formation was linearly decreased with increasing UDCA concentration. UDCA-induced apoptosis was completely blocked by z-IETD, z-LEHD, and z-VEID, and partially suppressed by z-DEVD. In accordance with this, UDCA activated caspases (3, 6, 8, and 9), indicating that UDCA induces extrinsic and intrinsic apoptotic pathways. In SNU601, UDCA increased ERK1/2 phosphorylation, not affecting p38MAPK or JNK activity. Unexpectedly, suppression of ERK pathway by PD98059, or U0126 significantly decreased UDCA-triggered apoptosis. We examined whether some membrane events are involved in the UDCA-induced cell death. Imipramine, A-SMase inhibitor strongly suppressed UDCA-induced apoptosis, indicating that UDCA-induced apoptosis is mediated through A-SMase activation. Prevention of ERK decreased UDCA-induced SMase activation, but inhibition of A-SMase activity did not affect ERK activation. These results suggest that ERK activation is an upstream event of SMase activation.
Conclusion(s) UDCA induces apoptosis by activating ERK1/2 – A-SMase pathway in SNU601 gastric cancer cells.

P4.107
Expression of human MxA protein in liver cirrhosis and in primary & secondary liver cancers

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Background Human MxA protein is under the transcriptional control of type I interferons and it was shown to be up-regulated in hepatitis C virus related hepatocellular carcinoma (HCC) (Chaerkady, JProteome Res 2008) as compared to surrounding tissue. We compared the expression of MxA protein by immunohistochemistry in liver

cirrhosis (Ci), hepatocellular and chloangiocellular carcinoma (CCC) and in metastatic colon cancer (MCC).

Methods A total of 67 retrospective paraffin embedded surgical sections were stutied. MxA protein was visualized by monoclonal antibody (Hochkeppel, NovartisPharma, Basel) or rabbit antiserum (Julkunen, NPHI, Helsinki) and visualized using DAKO DAB+ Envison kit. Omission of the first antibody or irrelevant antibody was used as negative control. Each entire slide was evaluated and assigned a score for frequency & intensity; total score was then calculated by multiplication.

Results The majority of the hepatocytes expressed diffuse cytoplasmic staining of high intensity. The neoplastic cells showed less frequent and intense staining. There was significantly lower total score for MxA expression in HCC than in surrounding cells (paired t-test, p=0,0005). Mean score±SD for hepatocytes for Ci(22), HCC(25), CCC(8), MCC(12) were: 10.7±3.2; 12.4±1.6; 12.4±2.8; 11.0±3.4 respectively. Mean score± SD for neoplastic cells for HCC(25), CCC(8), MCC(12) were: 7.6±3.9; 8.3±3.8; 6.5±4.01 respectively. Unpaired comparisons showed significant differences between normal and neoplastic cells in HCC (p=0.001) and MCC (p = 0.003), but not in CCC.

Conclusion(s) The discrepancy between the proteomics and our IHC study can be explained, either by derangement of translation of MxA protein in HCC, or by patient selection bias.

P4.108

"Forgotten organs" for metastases

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Background The ability to migrate and invade into surrounding tissues, blood, and lymphatic vessels is one of the halmarks of cancer and a prerequisite for local tumor progression and metastatic spread. However, the underlying mechanisms controlling cell invasiveness remain poorly understood.

Methods We analyzed the histological parameters and immunohistochemical expression in 6 metastatic tumors of the unusual localizations.

Results (1) autopsy case: Sudden cardiac death, 40 days after removal of the original hyroid carcinoma. Intramyocardial tumour nodules of the right atrium and ventricular septum were macroscopically seen. Abdominal granullar cell ovarian metastasis found after 23 years from its diagnosis and surgical therapy. (3) Splenic subcapsular metastasis of the ovarian cystadenocarcinoma, was ressected after four years from its cytologic diagnosis in the massive ascites. (4) An 17 year- old boy, had sigmoid colon metastasis of choriocarcinoma of the testis. (5) Gastroduodenal mucosa and submucosa were infiltrated with epitheloid melanoma of the eye. (6) A 46-year -old woman, had signet ring cell breast tumor metastatic from the stomach.

Conclusion(s) We point out the four pathways of invasion : retrograde lymphatic extension, hematogenous spread, direct contiguous extension and transvenous extension. But, the pathway of invasion, as well as the time of invasion, often are not predictable.

P4.109

Genetic and epigenetic alterations in sporadic basal cell carcinomas

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Background Recently it has become evident that along with genetic mutations epigenetic alterations, a mechanism for tumor suppressor gene inactivation, seem to play a key role in the pathogenesis of human cancer. We searched for epigenetic alterations of hMLH1, RASSF1A, DAPK, APC, DCR1 and DCR2 genes and B-Raf mutations in Basal Cell Carcinomas (BCC) in association to the clinicopathological parameters and the histological subtypes of the tumours.

Methods Fifty BCCs were analysed by methylation-specific PCR (MSP) in order to assess the methylation status of hMLH1, RASSF1A, DAPK, APC, DCR1 and DCR2 genes after sodium bisulfite treatment of the tumour DNA. hMLH1 and DCR1 gene expression was investigated by immunohistochemistry. B-Raf mutations were studied by High-Resolution Melting analysis (HRM).

Results High frequency of promoter methylation occurred in DCR1 (32%), DCR2 (44%), RASSF1 (32%) and APC (32%) genes whereas methylation of DAPK was moderate (15%) and methylation of hMLH1 was absent. No B-Raf V600E mutation was detected. There was no correlation between the frequency of the promoter methylation of the above mentioned genes and the clinicopathological features or the histological subtypes of the tumours.

Conclusion(s) The high frequency of RASSF1A, DCR1, DCR2 and APC genes methylation may suggest that methylation may be an important pathway in the tumorigenesis of BCC given that there is a potential relationship between methylation and exposure to solar UV-radiation which is the main cause of BCC development. Nevertheless, further studies are mandatory to elucidate the above mentioned conclusion.