resistance, suggesting a novel strategy for increasing NGEN sensitivity in Bcl-2 overexpressing human leukemia cells.

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Cancer inhibition by normal differentiated cells

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Background: The stem cell theory of cancer states that tumor development is originated in a mutated stem or progenitor cell. Stem cells are susceptible of inhibition when there is no need to proliferate and have the same regulatory pathways as tumor cells. These facts allow us to hypothesize that tumor as well as stem cells could be inhibited by normal differentiated cells.

Materials and methods: In our study, we used Balb-c nude mice and MCF-7 breast cancer cells. The nude mice were divided in two groups (n=10), the control group (CG) and the test group (TG), whose mice were submitted to an epithelial removal. The animals of both groups were subcutaneously injected with β-estradiol and progesterone, every day, for three weeks, to simulate the pregnancy full differentiation of the mammary gland. Afterwards, 2 million of MCF-7 cells were injected in the mammary gland (CG) and in the cleared mammary fatpad (TG), in the respective group. Five weeks later, the tumors were removed and their volumes evaluated.

Results: The median volume of the tumors in the TG (64,6mm^3) was superior to the median volume in the CG (5,9mm^3) with a statistical significance (p = 0,003), using the Mann-Whitney test.

Conclusions: Our results demonstrate that there is an inhibition of tumor development by normal mammary epithelial cells, when we use the MCF-7 tumor cell line. They also strengthen our previous hypothesis about the existence of an inhibitory stimulus of normal cells in the carcinogenesis process and may elucidate different unexplained mechanisms, namely the protective role of pregnancy in breast cancer or the graft-versus-leukemia effect in haematological malignancies.

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Detection of deleted malignant brain tumors 1 and runt-related transcription factor 3 gene expressions in bladder carcinoma

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Background: Bladder cancer, comprises 3% of cancer among women and 7% of men, is the second most common malignancy of the genitourinary system is the fourth most common cause of death from cancer in men and eighth most common in women. Deleted in Malignant Brain Tumors 1 (DMBT1) gene, located at chromosome 10q25.3-q26.1 is highly expressed in alveolar and macrophage tissues. Some alterations in DMBT1 gene are caused in gliomas. Despite, a loss or reduction of DMBT1 expression in various cancers including gastric, colorectal, brain, lung and esophageal cancers, it has not been reported in bladder cancers. Runt-related transcription factor 3 (RUNX3) is a candidate tumor suppressor gene, a Runt domain transcription factor involved in TGF-β signaling. It is localized on the chromosomal region 1p36. RUNX3 gene expression in bladder carcinogenesis is particularly unknown. We aimed to evaluate DMBT1 and RUNX3 gene expression profiles in bladder cancer and how their expressions could be related to carcinogenesis in the bladder and their correlation with clinicopathological parameters.

Material and Methods: Fifty-six paraffin embedded specimens of transitional cell carcinoma of the urinary bladder were used in the study. Total RNA was extracted from bladder specimens and cDNA was synthesized. The quantification of DMBT1 and RUNX3 mRNAs were succeeded according to the manufacturers' instructions by using Lightcycler instrument.

Results: DMBT1 and RUNX3 gene expressions were identified in 100% of bladder carcinoma samples. No significant association was found in these genes expression levels when compared to sex and age. RUNX3 gene expression was decreased non-significantly in high-grade tumors. When DMBT1 gene expression was compared to tumor grades, a significant decrease was detected between grade I and III (p=0,028). We compared the expression results between patients' sex, age, pathologic degree and grades. We found that DMBT1 gene expression was decreased when grade was increased in this research.

Conclusion: A correlation was found between the DMBT1 gene expression and tumor grades. Expressions of tumor suppressors like DMBT1 and RUNX3 genes could be used as diagnostic markers in early detection and prognosis of the bladder cancer. Furthermore, detailed studies including these genes should be performed in protein levels in a large scale study.

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Expression of calreticulin in breast and cervical cancer in relation to clinical outcome

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Calreticulin is chaperone protein of endoplasmic reticulum, found in the cytotoxic granules of lymphocytes and natural killer cells. It is released with granzymes and perforin upon recognition of target cells. Contrary to its previous defined function in efficient interaction between cytotoxic and target cells, it is shown in recent studies that tumor spread could be influenced by calreticulin, which is overexpressed in some cancer cell lines and in some tumors. It is also shown that calreticulin may induce tumor progression, because at the concentration of 2,2 x 10-7 M it completely blocks perforin-mediated lysis, by stabilizing membranes preventing polyperforin pore formation. The purpose of this study was to investigate whether the expression of calreticuiln in breast and cervical cancer exists and, if so, whether that expression is related to clinical outcome and tumor progression. In this study 33 patients with breast cancer and 25 patients with cervical cancer were included. Patients with breast cancer underwent surgery, while cervical cancer patients were treated by radiotherapy. Clinical outcome was evaluated for two years for breast cancer patients and for one year for cervical cancer patients. Expression of calreticulin was determined prior to clinical treatment, by immunohistochemistry, using rabbit anti-calreticulin polyclonal antibody, according to manufacturer recommendation. Among 22/33 breast cancer patients who had expression of calreticulin, three of them developed distant metastases. On the other side, among 12/25 cervical cancer patients with calreticulin expression, four of them had progressive disease. It has to be noticed that those progressive cancer patients with calreticulin positivity were also the only patients with progressive disease in both observed groups of patients. Namely, all patients with progression of malignant disease expressed tumor positivity for calreticulin. Our findings support the state that calreticulin can regulate lytic and cytotoxic function. These preliminary results indicate the need for further investigation related to the role of calreticulin in malignant behavior.

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Over-expression of PRKAR1A in hepatic progenitor cells during cholangiocarcinogenesis induced by liver fluke (Opisthorchis viverrini)

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Background: PRKAR1A, a regulatory subunit of protein kinase A type I (PKA I) which plays a crucial role in cell proliferation and differentiation was found to be overexpressed in cholangiocarcinoma (CCA). To clarify the role of PRKAR1A in cholangiocarcinogenesis, we have studied the expression of PRKAR1A in Opisthorchis viverrini (Ov) and N-nitrosodimethylamine (NDMA) induced CCA in hamster model. Materials and Methods: Syrian golden hamsters were treated with Ov and NDMA to induce CCA and were sacrificed on weeks 1, 4, 12 and 24. The immunofluorescence technique was used for localizing PRKAR1A, PCNA and glypican-3 in liver tissues.

Results: PRKAR1A positive staining was markedly increased in hyper-proliferating bile duct epithelial cells indicated by a proliferating marker PCNA observed for liver tissues that belonged to hamsters induced from weeks 12 to 24. PRKAR1A were prominently positive at week 24 as tumor developed in tumor cells. Interestingly, the liver progenitor cell marker, glypican-3 was coexpressed in PRKAR1A positive tumor cells.

Conclusions: Our result indicates that PRKAR1A may regulate cellular hyper-proliferation triggered by the liver fluke and plays role in cholangiocarcinogenesis by induced the aberrant proliferation and differentiation of hepatic progenitor cells.