P13

DNA methylation in serum of breast cancer patients: An independent prognostic marker

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Changes in the status of DNA methylation are one of the most common molecular alterations in human neoplasia. Because it is possible to detect these epigenetic alterations in the bloodstream of patients, we investigated whether aberrant DNA methylation in patient pretherapeutic sera is of prognostic significance in breast cancer. Using MethyLight, a high-throughput DNA methylation assay, we analyzed 39 genes in a gene evaluation set, consisting of 10 sera from metastasized patients, 26 patients with primary breast cancer, and 10 control patients. To determine the prognostic value of genes identified within the gene evaluation set, we finally analyzed pretreatment sera of 24 patients having had no adjuvant treatment (training set) to determine their prognostic value. An independent test set consisting of 62 patients was then used to test the validity of genes and combinations of genes, which in the training set were found to be good prognostic markers. In the gene evaluation set we identified five genes (ESR1, APC, HSD17B4, HIC1, and RASSF1A). In the training set, patients with methylated serum DNA for RASSF1A and/or APC had the worst prognosis ($P < 0.001$). This finding was confirmed by analyzing serum samples from the independent test set ($P = 0.007$). When analyzing all 86 of the investigated patients, multivariate analysis showed methylated RASSF1A and/or APC serum DNA to be independently associated with poor outcome, with a relative risk for death of 5.7. DNA methylation of particular genes in pretherapeutic sera of breast cancer patients, especially of RASSF1A/APC, is more powerful than standard prognostic parameters.

P14

Polyunsaturated fatty acids sensitise colon cancer cells to the apoptotic effects of sodium butyrate

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Dysregulation of the balance between cell growth and death in the colonic epithelium is associated with cancer promotion. Understanding how cell death in this self-renewing tissue is regulated and how it is influenced by interaction of specific dietary components, especially fat and fibre, could lead to improved treatment and prevention strategies for cancer. The important modulators of cytokinetics in the colonic epithelium are short-chain fatty acids, particularly butyrate, produced from dietary fibre. Supply of essential polyunsaturated fatty acids (PUFAs) of n-6 and n-3 types from dietary fat is proposed to be linked with the risk of colorectal cancer Therefore, in our experiments the effects of two types of PUFAs - arachidonic (AA, 20:4, n-6) or docosahexaenoic (DHA, 22:6, n-3) - on the response of human colon adenocarcinoma HT-29 cells to sodium butyrate (NaBt) were investigated. The parameters reflecting cell proliferation and cell death were studied together with oxidative response, mitochondrial membrane potential (MMP) and changes of selected regulatory molecules associated with cell cycle (p27Kip1and p21Cip1/WAF1) and apoptosis (caspase-3, -9,PARP, Bcl-2, Bax, Bak, Mcl-1). After 48 h of treatment with either AA or DHA a significant increase of the corresponding PUFA in HT-29 cell lipids was observed. These cells were more sensitive to NaBt-induced apoptosis reflected by an increased % of floating cells, cells in subG0/G1 population, and cells with apoptotic morphology. This was associated with increased reactive oxygen species production, lipid peroxidation, decrease of MMP, activation of caspase-3 and -9, PARP cleavage, and changes in the expression of antiapoptotic Mcl-1 protein. Pre-treatment of cells with PUFAs attenuated cell cycle arrest caused by NaBt associated with increased p27Kip1 expression. The observed effects were modulated after inhibition of protein synthesis by cycloheximide, and only partially by the antioxidant Trolox. Taken together, PUFAs may have beneficial effects in the colon enhancing apoptosis induced by NaBt. Alteration of cell membrane lipid composition and potentiation of oxidative processes accompanied by changes in mitochondria followed by stimulation of apoptotic cascade components play a role in these effects. This work was supported by the Grant Agency (GA) of the Czech Rep (No. 524/04/0895) and GA of Academy of Sciences of the Czech Rep. (No. S5004009).

P15

The use of artificial neural network in identification of women with high risk for breast cancer

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Introduction: Breast cancer is the leading malignancy in females. So far, early detection is the best possible method for the control of this disease. Screening recommendations, presented by leading cancer organizations, agree on mammography being the screening method; however, there is no overall consensus over the screening interval and the age of women offered screening.

Objective: Individual risk for breast cancer in women within the same age group might differ significantly depending on family history and other factors. Identification of individual risk for breast cancer might enable early detection scheme adapted to women’s personal risk. METHODS In this paper the model based on Artificial neural network (ANN) is presented; the aim of this model is the identification of women at high risk for breast cancer based on risk factors. ANN models are particularly convenient for identification of systems with high number of variables. The work with ANN consists of 3 phases: (a) neural network architecture selection - number of units and layers of ANN; (b) model parameter estimation; and (c) model verification - testing the model by set of test patterns.

Results: As input data for ANN model we used data on risk factors (age, family history, age at menarche, age at menopause,

age at first delivery etc.) and symptoms for breast cancer. The model was based on data of two main groups (group of women with breast cancer and the control - healthy group). The verification of the model performed on set of 100 test patterns. Accuracy of identification of high-risk group was 98%.

Conclusion: Advantage of this model is quick and easy identification of women with high risk for breast cancer enabling individually tailored prevention of the disease.

P16

A case-control study on the role of blood group and family history in developing gastric cancer before the age of 50

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Introduction: Development of gastric cancer (GC) before 50 is likely to have a genetic basis. Blood group A has been shown as a risk factor for GC. Some parts of Iran are endemic regions for GC.

Aims & methods: In this prospective case-control study, we enrolled Iranian gastric cancer patients under the age of 50 and sex-matched controls over 50. All the patients and (if alive)/or their family members were interviewed and their pedigrees were drawn. The blood group of the patients were also tested or obtained from the in-patients records.

Results: 54 cases (mean age: 37.1, 18-49; m/f=1) under 50 years old and 54 sex-matched controls (mean age: 68.2, 50-88) were enrolled in the study. 40.7% of the study group were dead and 59.3% were alive at time of study. Distribution of blood groups is as follow: 68.6% O, 13% A, 13% B and 5.4% AB in cases and 27.7%, 63%, 6.5% and 2.7% in controls, respectively. 50% of the cases and 9% of controls had some first or second-degree relatives with gastric or other types of cancers ($p<0.01$). Breast, lung, gynecological and hematological malignancies constituted other type of cancer in their families.

Conclusion: It seems that gastric cancer before 50 is accompanied with a familial aggregation. Interestingly, our study shows the significant correlation between blood group O and the development of gastric cancer under 50. This arises the need for more linkage analysis study on the role of blood group genetic area in familial aggregation of gastric cancer.

P17

The role of clinico-genetic monitoring of risk groups for early diagnostics of female reproductive system tumors

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The oncoepidemiologic situation in Ukraine is marked by the continuous increase of female reproductive system tumors. More than 50% of the new diagnosed cases depend on the influence of external and internal factors. The risk of developing the similar disease in healthy relatives (mother, sister, daughter) of the patients with cancer is about 50%. We performed clinical and genealogical analysis of 513 healthy women, 44% of them had relatives with benign and malignant tumors. Clinical and genealogical analysis, performed in 520 probands with ovarian cancer revealed 34 families with 2 or more relatives suffering from cancer (6.54%). 81 patients with ovarian cancer had 1 close relative with tumors (15.57%). The similar analysis was conducted in genealogies of 482 probands with endometrial cancer. It revealed 13 families with 2 or more relatives suffering from cancer (2.69%). 49 patients with endometrial cancer had 1 close relative with tumors (10.2%). Frequently the relatives of patients with ovarian and endometrial cancers suffered from tumors of female reproductive sphere combined with gut tumors. We examined 110 close relatives of patients with ovarian and endometrial cancer who had an increased risk of developing tumors. Only 19 women manifested with the female reproductive system disorders at the time of their first consultation. The other 91 women were practically healthy. It should be stressed that the risk of developing cancer was 52-54% in the examined women. During a 3-year follow-up of these patients we diagnosed benign tumors, precancrous diseases of female reproductive system and the disorders that were unfavorable for tumor development: myoma of the uterus – 8, ovarian cysts and cystomas – 7, nodular and diffuse mastopathies – 29, tuboovarian tumors – 5, endometrial hyperplasia – 9, chronic adnexitis – 11. This approach is effective because it became possible to diagnose ovarian and endometrial cancers 4 women of the group with the increased genetic risk quite early (sisters of the probands with ovarian cancer – highly differentiated endometrial adenocarcinoma IIa; daughter of the proband with ovarian cancer – serose ovarian cystadenocarcinoma Ib; sister of the proband with endometrial cancer – ovarian cystadenocarcinoma I). The suggested approach to the prevention and early diagnostic of female reproductive system tumors has clinical and social benefits. It could be recommended as a model to the creation of the system of the oncogenetic help to the population.

P18

The dependence of VEGF level from characteristics of Lewis lung carcinoma development in C57BL6 mice

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Targeting angiogenesis represents a new strategy for the development of cancer prevention. Angiogenesis,or new blood vessel growth from an existing vasculature,expression of vascular endothelial cell growth factor (VEGF), has become a veri promising target for experimental therapies in cancer. The aim of the study was to investigate dependence of VEGF level from characteristics of Lewis lung carcinoma (LLC) development in C57BL6 mice for the use in perspective as experimental model for the screening new antiangiogenic agents. LLC transplantation was performed by injection i.m. of 0.02 ml of the tumor cell suspension of 2×10^5 cells. For monitoring of the primary tumor, the levels of tumor dissemination, the tumor volumes (VT, mm^3), the number and volumes of the lung metastasis (VLM, mm^3), and VEGF levels in serum were estimated.