patients, 95 ovarian cancer patients and 205 control subjects, for *XPD* exon 10 polymorphism using PCR-RFLP.

Results: We found AA variant genotype in 15,8% of ovarian cancer patients and 6,8% of healthy group. We observed that carriers of *XPD* exon 10 AA genotype have increased susceptibility of ovarian cancer (OR=2,57 95% CI 1,19-5,59; p=0,017), especially before the age of 53 years (OR= 3,87 95% CI 1,39-10,81; p= 0,010). Sixteen percent of cases of ovarian cancer cases younger than 53 could be attributed to the influence of this risk factor. We found AA variant genotype in 9,5% of breast cancer patients and 6,8% of healthy group. We did not find any association between *XPD* exon 10 polymorphism and breast cancer risk (OR= 1,44 95% CI 0,70-2,96; p= 0,319), even when we considered age of onset (47 years).

Conclusions: Our results suggest an important role for *XPD* exon 10 polymorphisms in the susceptibility to ovarian cancer. Further studies will help to confirm the influence of these genotypes in the determination of chemoprevention strategies, and its role in prognostic and response to chemotherapy.

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UGT1A1 polymorphisms correlate with adverse side effects and clinical response in metastatic colorectal cancer patients treated with Irinotecan

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Background: Irinotecan (CPT-11) is metabolized by esterase to form a SN-38, which is further conjugated by UGT1A1. A genetic polymorphism related to its enzymatic activity has been identified in the promoter region of the UGT1A1 gene. Individuals with an additional TA repeat in this region may be at increased risk of Irinotecan toxicity.

Material and Methods: Fifty eight patients with metastatic colorectal cancer (MCRC) were included in the study. Eleven patients were treated with CPT11; nine with CPT11 + Tomudex and thirty eight patients with CPT11 + 5FU. DNA extraction and UGT1A1 genotype were performed using previously described methods. We investigated the differences in the development of adverse side effects (grades III-IV diarrhea, neutropenia and asthenia), termination of therapy, reduction of dose intensity and clinical response, depending on the genotypes of UGT1A1 in MCRC patients treated with Irinotecan.

Results: Twenty patients (47%) were TA6/TA6; 25 patients (43%) were TA6/TA7, and 6 patients (10%) were TA7/TA7. All six homozygote 7/7 cases showed grade > III toxicity (4 cases diarrhea; 1 case asthenia, fever and bad performance status, and 1 case with neutropenia). Fifteen out of 25 (60%) heterozygous 6/7 cases showed grade III-IV toxicity (11 cases diarrhea and/or neutropenia; 3 cases with asthenia and bad performance status, and 1 case with septic shock due to pneumonia). Six out of 27 patients (22%) with a normal genotype 6/6 developed side effects (grade III-IV diarrhea and/or neutropenia). Termination of therapy or reduction of dose intensity had to be performed in 100% of patients homozygotes TA7/TA7, in 52% of patients with a TA6/TA7 genotype and in 22% of patients with a TA6/TA6 genotype. There was no mortality due to CT. Twenty one out of 27 patients,(78%)(95%-CI: 62%-93%), with severe toxicity had a homozygous or heterozygous UGT1A1 genotype. TA6/TA6 and TA7/TA6 patients had a better response rate and median time to progression than homozygous TA7/TA7 cases:36% and 27% vs 17%, and 8,3 months and 5,5 months vs 4 months, respectively.

Conclusions: The results suggest that the UGT1A1 genotype i) might be clinically useful for predicting severe toxicity in cancer patients treated with Irinotecan and ii) is related to the clinical response in the group of patients included in the study.

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Ha-ras oncogene induces the metastatic ability of transformed cells in vivo through RalGDS downstream signalling pathway.

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Background: Earlier a collection of v-src transformed cell lines were isolated as a result of independent infection of primary hamster fibroblasts with different stocks of Rous sarcoma virus. All lines had a typically transformed phenotype and were highly tumorigenic for the inoculated animals [Deichman et al. 1989]. However, remarkable differences were found in the metastatic activity of transformed cells: after s.c. injection the majority of cells within two months induced about 150 metastatic nodules in the lung and/or other organs of inoculated hamsters (high metastatic lines, HM). On the other hand, after s.c. inoculation of HET-SR cells (single low metastatic, LM) metastatic nodules were practically not observed. Amount of the v-src protein and its kinase activity were approximately equal in both HM and LM cell types. [Tatosyan et al., 1996]. Introduction of activated Ha-ras^{V12} oncogene into LM cells leads to significant stimulation of metastatic potential of recipient cells.

Material and Methods: v- src-transformed hamster fibroblasts with low metastatic potential. Transfection >f by different mutant variants of Ha-ras oncogene. Analysis of spontaneous (SMA s.c. injection of the cells) metastatic characteristics of the transfectants *in vivo*. Comparative immunoblot analysis of different signal transduction proteins supposed to be involved in metastatic processes.

Results: In order to identify intracellular signaling chains and proteins involved in the metastatic process of transformed cells we have used three different effector-loop mutant forms of Ha-ras each of which activates a single downstream effector pathways. ERK pathway selective protein $RasV^{12}35S$ had no effect on metastatic activity of transfected cells (no more than 3-4 nodules *per* animal). Identical results were obtained with transfected PI3K kinase pathway protein $RasV^{12}40C$. In contract the $RasV^{12}37G$ an activator of RalGDS was extremely effective *in vivo* inducing about 120 metastatic nodules. The production and tyrosine phosphorylation of several proteins, involved in major signal transduction pathways were compared in all transfected cell lines. No differences have been seen in Src, PI3K, PKB, MEK-1 and Rac-1 activity. At the same time the level of Rho and Rac production, as well, as the phosphorylation of ERK1/2 and were changed in cells, expressing different phenotype.

Conclusions: The described collection of new cell lines with modulated metastatic properties is unique model system for identification of specific genetic and molecular factors responsible for invasive and metastatic behavior of tumor cells. RalGDS downstream effector pathway has major contribution to metastatic properties of transformed cells. We found several intracellular signaling proteins modulating their activity according with metastatic phenotype.

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A cytogenic study of Burkitt's lymphoma cell lines; Daudi, Namalwa and Raji

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Introduction: Since 1960 and description of the Philadelphia chromosome in CLL, the association of specific structural and numerical chromosome abnormalities with certain types of malignancies has been appreciated. Relatively little progress has been achieved in the study of human lymphoma cell lines, especially the cytogenic changes and the degree of heterogeneity observed in different karyotypic variants of the subpopution of these cell lines. Therefore, the study of karyotypic evolution of lymphoma cells in direct preparations and on serial *in vitro* passages may be important in demonstrating karyotype stability under the new growth environment and to evaluate any cytogenetics evolution taking place during the *in vitro* establishment of the cell lines.

Materials and Methods: The cell lines were cultured in RPMI 1640 supplemented with 10% FBS and were subcultured every 3-4 days by dilution (1:4) of the culture medium. The cells were harvested by centrifugation after 2-3 days for Daudi and Raji and after 4 days for Namalwa cell lines. The cell pellets were resuspended in hypotonic solution and then fixed in the freshly made fixative. After preparing slides from the cells and trypsin treatment, the slides were stained in freshly prepared leishman's stain. The observed chromosomal abnormalities were then reported using ISCN 1995. In some cases FISH were applied to confirm results of G-bandings. In these cases mostly PCR amplified band specific fluorescent-labeled probes and for some abnormalities chromosome arm painting (CAP) probes were used.

Results: Chromosome analyses were successfully achieved on preparations from all cell lines. Overall analysis of the cell lines demonstrated that, in Daudi and Raji the chromosome number of majarity of the cells were 46, this number for Namalwa was 45. The most common chromosome abnormality detected in all cells analyzed was translocation between chromosome 8 and 14 with classical breakpoints (q24;q32), but many other abnormalities were also detected. The most important of these were additional material on the short arm of chromosome 11 (Daudi), additional material on the q35 of chromosome 4 (Raji) and an HSR attached to the long arm of one of the chromosome 1q (Namalwa) among others.